Department of Otorhinolaryngology and Head & Neck Surgery
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Infantile haemangioma and venous malformations: inheritance, risk factors, and treatment safety

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Academic Dissertation

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To my family

Ain’t no mountain high enough

- Nickolas Ashford &
Valerie Simpson

Contents

1. List of original publications

This thesis is based on the following original publications. The publications are reprinted with the kind permission of the copyright holders.

1. Castrén Eeva, Salminen Päivi, Gissler Mika, Stefanovic Vedran, Pitkäranta Anne, Klockars Tuomas. Risk factors and morbidity of infantile haemangioma: preterm birth promotes ulceration. *Acta Paediatr*. 2016 Aug;105(8):940-5. doi: 10.1111/apa.13460

2. Castrén Eeva, Salminen Päivi, Vikkula Miikka, Pitkäranta Anne, Klockars Tuomas. Inheritance Patterns of Infantile Hemangioma. *Pediatrics.* 2016. doi: 10.1542/peds.2016-1623.

3. Castrén Eeva, Aronniemi Johanna, Klockars Tuomas, Pekkola Johanna, Lappalainen Kimmo, Vuola Pia, Salminen Päivi, Pitkäranta Anne. Complications of sclerotherapy for 75 head and neck venous malformations. *European Archives of Otorhinolaryngology*. 2016 Apr; 273(4):1027-36. doi: 10.1007/s00405-015-3577-x.

4. Aronniemi Johanna, Castrén Eeva, Lappalainen Kimmo, Vuola Piia, Salminen Päivi, Pitkäranta Anne, Pekkola Johanna. Sclerotherapy complications of trunk and extremity venous malformations. *Phlebology*. 2015. doi: 10.1177/0268355515613740.

2. Abstract

Background and aims: Vascular anomalies constitute a challenging patient group. Their pathogenesis and risk factors are understood only in part. Their management has dramatically developed during the last 20 years. The objective of this study was to examine the mode of inheritance of and the risk factors for infantile haemangioma (IH), the most common vascular anomaly, and to analyse the treatment complications of sclerotherapy, the current first-line treatment for venous malformations (VM).

Patients and methods: For the IH studies, we included all IH patients who had visited Helsinki University Hospital's vascular anomaly clinic in 2004-2007. We collected data from hospital records on IH characteristics, complications, and interventions, and the child's perinatal data when available. We sent these patients and their caregivers a questionnaire on perinatal data, child's diseases, family history of IH, and the current subjective long-term discomfort due to IH. Perinatal and gestational data was compared to the Finnish Medical Birth Register data from the same catchment area in 2004-2007. Families reporting positive family history of IH were interviewed by phone to elucidate the pedigrees and inheritance patterns. For studies on sclerotherapy for VMs, we included all VM patients who had received sclerotherapy in our unit between 2007-2013. We recorded retrospectively VM characteristics, procedural data, and sclerotherapy complications, and analysed factors predisposing to complications. We graded complications from I to V according to the Clavien-Dindo classification for complications.

Results: In addition to known IH risk factors, this study showed that preterm birth promotes ulceration of IH. Maternal gestational diabetes mellitus rate was significantly higher in our IH cohort than in the catchment area of our hospital district. One-third of IH patients reported a positive family history of IH. The inheritance pattern followed the autosomal dominant pattern, but in ten families, the transmission may also have been maternal. IH characteristics were similar in familial and sporadic cases.

Of the head and neck venous malformations, 17% suffered from sclerotherapy complications. These patients needed overall more sclerotherapies, but also more surgery after sclerotherapy, and longer follow-up than those without a complication. Complication rate per procedure was 10%. Three treatment complications were severe, grade IIIb-IV, and necessitated surgical management and intensive post-complication care. Of the trunk and extremity VMs undergoing sclerotherapy, 24% suffered from complications. Complication rate per procedure was 13%. The use of ethanol and subcutaneous location predisposed to local complications. Four severe, grade IV to V complications occurred, one of which was lethal. Severe complications were related to blood coagulopathy.

Conclusions: Our results imply that the role of maternal gestational diabetes as a potential IH risk factor is unclear and deserves further studies. Preterm IH infants' higher risk for ulceration is a relevant concern for physicians treating IH-children. In addition to autosomal dominant inheritance, a relevant proportion of the familial IHs may be maternally transmitted. Complications of sclerotherapy for VMs mostly recover with conservative treatment, but severe complications do occur. Associated blood coagulopathy constitutes a major risk for the treatment. Interdisciplinary assessment of the treatment strategy is therefore crucial.

Tiivistelmä

Väitöskirjan tavoitteena oli selvittää infantiilin hemangiooman, lapsuusajan yleisimmän kasvaimen, riskitekijöitä ja perinnöllisyyttä, sekä tutkia skleroterapian, laskimoepämuodostuman ensilinjan hoitomuodon, turvallisuutta.

Hemangiooma-aineisto koostui potilaista, jotka olivat käyneet vuosina 2004-2007 Helsingin yliopistollisen keskussairaalan (HYKS) Lastenklinikan suoniepämuodostumapoliklinikalla. Potilastietojen ja kyselykaavakkeen perusteella selvitettiin hemangiooman ominaispiirteet, komplikaatiot, hoidot, muut sairaudet, raskaus- ja syntymätiedot, hemangiooman esiintyminen suvussa ja hemangioomasta aiheutuva myöhäishaitta. Potilaiden raskaus- ja syntymätietoja verrattiin Terveyden ja hyvinvoinnin laitoksen syntymärekisterin tietoihin. Perinnöllisten hemangioomatapausten perheet haastateltiin periytymismallien tunnistamiseksi. Tutkimuksessa havaittiin, että ennenaikainen syntymä altistaa hemangiooman haavautumiselle. Tunnettujen riskitekijöiden lisäksi havaittiin, että hemangioomalasten äideillä oli esiintynyt enemmän raskausdiabetesta verrattuna syntymärekisterin tietoihin. Kolmasosalla potilaista esiintyi hemangioomaa suvussa. Hemangiooman ominaispiirteissä ei ollut eroa perinnöllisten ja ei-perinnöllisten tapausten välillä. Hemangiooma periytyi pääasiallisesti autosomissa vallitsevasti. Tutkimuksessa havaittiin lisäksi sukuja, joissa periytymismalli saattoi olla maternaalinen eli äidiltä periytyvä.

Laskimoepämuodostuma-aineisto koostui HYKS:ssa vuosina 2007-2013 skleroterapialla hoidetuista potilaista. Sairaalan rekisteristä analysoitiin retrospektiivisesti komplikaatiolle altistavia tekijöitä. Komplikaatiot arvioitiin Clavien-Dindo -luokituksen mukaan. Skleroterapiaan liittyviä komplikaatioita esiintyi 17%:lla pään ja kaulan laskimoepämuodostumapotilaista, joista 4%:lla komplikaatiot olivat vakavia. Hoitokertakohtainen komplikaatioriski oli 10%. Komplisoituneissa tapauksissa tarvittiin enemmän hoitokertoja ja skleroterapian jälkeistä kirurgiaa verrattuna komplisoitumattomiin tapauksiin. Raajojen ja vartalon laskimoepämuodostumapotilaista 24%:lla esiintyi komplikaatio skleroterapiassa. Hoitokertakohtainen komplikaatioriski oli 13%. Etanolin käyttö skleroterapiassa sekä epämuodostuman ihonalainen sijainti altistivat paikallisille komplikaatioille. Seuranta-aikana esiintyi neljä henkeä

uhkaavaa komplikaatiota, jotka johtuivat vakavasta hyytymisjärjestelmän häiriöstä. Yhdessä tapauksessa vaikea hyytymiskomplikaatio johti potilaan kuolemaan.

Tämän väitöskirjan osatöiden perusteella todetaan, että ennenaikaisesti syntyneet lapset ovat alttiimpia hemangiooman haavautumiselle. Raskausdiabeteksen yhteys lapsen riskiin saada hemangiooma vaatii lisäselvityksiä. Perinnöllisyystutkimusten perusteella hemangiooma saattaa periytyä sekä autosomissa vallitsevasti että maternaalisesti. Skleroterapia on pääasiallisesti turvallinen hoitomuoto laskimoepämuodostumaan. Etanolin käyttöä skleroterapiassa tulee välttää. Laskimoepämuodostumaan liittyvä hyytymishäiriö voi altistaa potilaan henkeä uhkaavalle hoitokomplikaatioille.

3. Abbreviations

ATII: Angiotensin II
AVM: Arterio-venous malformation
CH: Congenital haemangioma
CI: Confidence interval
CM: Capillary malformation
CVS: Chorionic villus sampling
DIC: Disseminated intravascular coagulopathy
EPC: Endothelial progenitor cells
FMBR: Finnish Medical Birth Register
GDM: Gestational diabetes mellitus
GLUT-1: Glucose transporter protein isoform 1
H&N: Head and neck
HUH: Helsinki University Hospital
ICD: International Classification of Diagnosis
IH: Infantile haemangioma
ISSVA: International Society for the Study of Vascular Anomalies
IVF: *In vitro* fertilization therapy
KHE: Kaposiform haemangioendothelioma
LM: Lymphatic malformation
LMWH: Low-molecular-weight heparin
LUMBAR: Lower body infantile haemangioma, urogenital anomalies, myelopathy, bony deformities, anorectal malformations and arterial anomalies, renal anomalies
MRI: Magnetic resonance imaging
NICH: Non-involuting congenital haemangioma
OR: Odds ratio
PDL: Pulse dyed laser
PE: Preeclampsia
PHACES: Posterior fossa malformations, haemangioma, arterial anomalies–cardiac defects, eye abnormalities, sternal cleft and supraumbilical raphe syndrome
PICH: Partly-involuting congenital haemangioma
RAS: Renin-Angiotensin system
RICH: Rapidly involuting congenital haemangioma
STS: Sodium tetradecyl sulphate
T&E: Trunk and extremity
TA: Tufted angioma
THL: Finnish National Institute of Health and Welfare
US: Ultrasonography
VAS: Visual analogue scale
VEGF: Vascular endothelial growth factor
VM: Venous malformation

4. Introduction

Congenital vascular anomalies constitute a diverse group of mostly benign vascular lesions mainly occurring in children and adolescents (1,2). These anomalies are divided into vascular tumours and vascular malformations (1-5). The most common vascular tumour is infantile haemangioma (IH), and the most common vascular malformation is venous malformation (VM) (1,4,6-9). Vascular anomalies typically reside in the head and neck area (4,10,11). Clinical image of vascular anomalies varies dramatically from small innocuous vascular lesions to large, diffuse, invasive vascular lesions that may cause substantial disfigurement, functional problems, coagulopathy, and severely disturb the cardiovascular system (4). Therefore their treatment strategy highly depends on the diagnosis and the extent of morbidity they cause.

For IH, risk factors are relatively well documented, but the genetic background remains largely unsolved (6,9,12,13). For VMs, the TIE2 mutation, and some other genetic alterations are causative in most patients (10,14). Because most vascular anomalies are benign, to guarantee treatment safety is essential.

This dissertation will focus on the most common vascular anomalies: infantile haemangioma and venous malformation. The first main objective is to study the risk factors and inheritance of IH. The second main objective is to study the complications of sclerotherapy, the current first-line treatment for VMs.

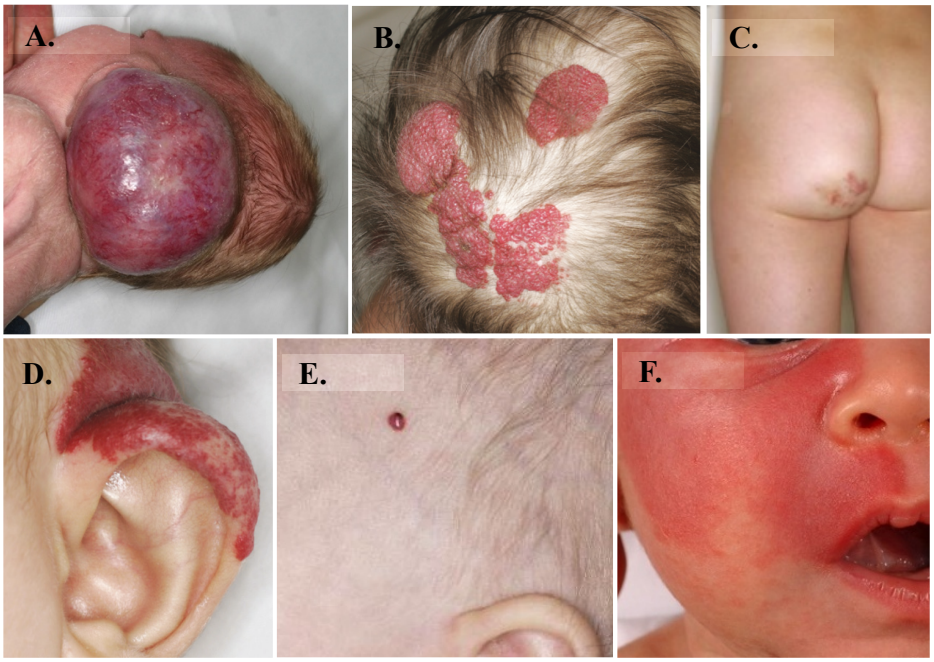
5. Review of the literature

5.1. Overview of vascular anomalies

5.1.1. Terminology and classification

The term ‘Vascular anomaly’ covers a large, heterogeneous group of vascular lesions and birthmarks that range from innocuous lesions to large, life-threatening vascular masses causing severe discomfort, organ dysfunction, cardiac compromise, and coagulopathy (1,4). The nomenclature for vascular anomalies has long been inaccurate, leading to misunderstanding, improper or delayed diagnosis and treatment. The terms ‘haemangioma’, ‘cavernous or capillary haemangioma’ have been applied to a variety of vascular lesions that actually imply other vascular lesions than the typical infantile haemangioma. Figure 1 shows different vascular anomalies. Expanding knowledge of vascular anomalies and systematic work of interdisciplinary vascular anomaly teams has led to a more precise classification system (1,2,5,15-17).

Figure 1. Various types of vascular lesions. A. Congenital haemangioma. B. Infantile haemangioma. C. Lymphatic malformation. D. Infantile haemangioma. E. Pyogenic granuloma. F. Capillary malformation.



Mulliken and Glowacki introduced the first classification of vascular anomalies based on their endothelial and growth characteristics that distinguished vascular tumours and malformations in 1982 (1-3). Thereafter, this classification has been updated several times due to the increasing understanding of vascular anomalies (5,18,19). The current classification, established by the International Society of the Study of Vascular Anomalies (ISSVA), was updated in 2014, and is summarised in Table 1 (5). As an advantage compared to previous updates, the classification now takes into account not only the cellular and growth characteristics, but also the behaviour of the lesion. The ISSVA classification functions as a framework for the diagnostic challenges, and it should evolve by means of constantly expanding knowledge (5). Due to scarcity of knowledge, a group of vascular anomalies still remain unclassified, such as verrucous haemangioma, angiokeratoma, and angiomatosis of soft tissue, the latter also called PTEN hamartoma, due to its PTEN mutation (5).

Table 1. Classification of vascular anomalies adapted from the ISSVA 2014 classification (5). Reprinted with the permission of the American Academy of Pediatrics, from Wassef et al. "Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies." Pediatrics. 2015 Jul;136(1):e203-14.

Classification of Vascular Anomalies					
Behaviour	**Vascular Tumours**	**Vascular Malformations**			
		Simple	**Combined**	**Of Major Named Vessels**	**Associated with other anomalies**
Benign	IH CH Tufted angioma Pyogenic granuloma Others	CM			
Locally Aggressive or Borderline	Kaposiform haemangio-endothelioma Others	VM LM	CM+VM CM+LM CM+LM+VM LM+VM	Truncu-lar	Klippel-Trenaunay Parkes-Weber (CM+AVF) Sturge-Weber (CM) Others
Malign	Angio-sarcoma Kaposi sarcoma Ephitelioid haemangio-endithelioma	AVM AVF	CM+AVM CM+LM+AVM CM+VM+AVM		CLOVES Others

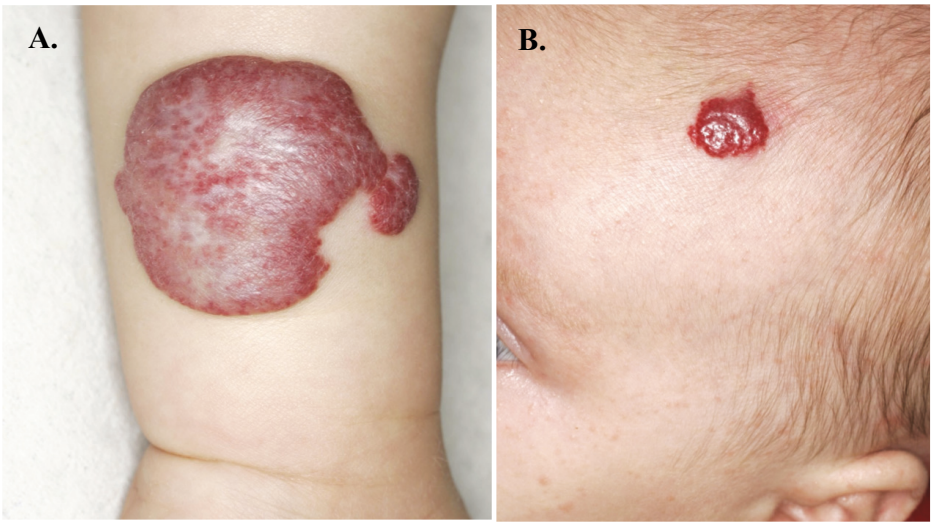
Abbreviations: AVF: Arteriovenous fistula; AVM: Arteriovenous malformation; CH: Congenital haemangioma; CLOVES: Congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi and spinal or skeletal anomalies; CM: Capillary malformation; IH: Infantile haemangioma; LM: Lymphatic malformation; VM: Venous malformation

5.1.2. Vascular tumours

Vascular tumours are characterized by endothelial proliferation and by aberrant blood vessel growth and architecture (1-3). The most common vascular tumour is infantile haemangioma (IH), which is the most common tumour of childhood (Figure 2) (1,4). Histologically IH is distinct from other benign vascular tumours and malformations: only IH stains positive with glucose transporter protein isoform 1 (GLUT1) antigen

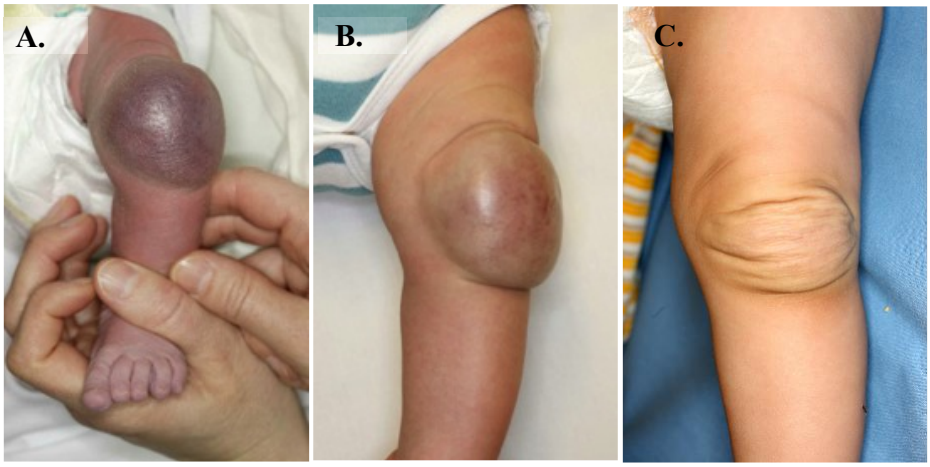
(20). For the epidemiology, pathogenesis, clinical course, associated syndromes, and management of infantile haemangioma, see section 5.2. In addition to IH, other vascular tumours comprise congenital haemangioma, pyogenic granuloma, tufted angioma, and haemangioendothelioma (2,5,18).

Figure 2. Typical infantile haemangioma of the arm, A., and forehead, B.



Congenital haemangioma (CH) differs from IH in its histopathology and its growth characteristics: CH is fully developed at birth, after which it can follow three different involution patterns. Rapidly involuting congenital haemangioma (RICH) starts to involute shortly after birth, reaching full involution by the first year of life (Figure 3) (21). Non-involuting congenital haemangioma (NICH) represents the other extreme of congenital haemangioma, as it is fully formed at birth, but it neither involutes nor grows thereafter (22,23). Some congenital haemangiomas show some but not full involution and are categorized as partly-involuting congenital haemangiomas (PICH) (24,25). Congenital haemangiomas are less prevalent than IHs. All CHs stain negative with GLUT1 (26). RICH, when large in volume, can sometimes lead to transient thrombocytopenia and cardiac compromise (27).

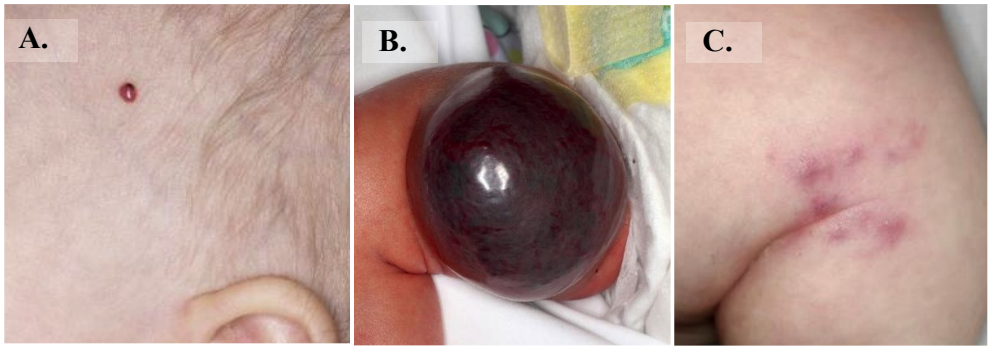
Figure 3. Rapidly involuting congenital haemangioma after birth, A., at age 5 months, B., and at age 12 months, C.



Pyogenic granuloma is defined as a reactive, acquired, proliferative vascular lesion, often appearing in the head and neck region (Figure 4A). It grows quickly to its maximal size and often manifests a pedunculated base. Almost half of all pyogenic granulomas appear during the first 5 years of life (28).

Tufted angiomas (TA, Figure 4C) are benign vascular tumours, mostly located in the neck or upper thorax. TAs sometimes mimic IH; however, they neither show such clear growth and involution pattern as IH nor do they stain with GLUT1 antigen (26,29,30). Kaposiform haemangioendothelioma (KHE, Figure 4B) is a locally aggressive vascular tumour that like a TA, exhibits an unpredictable growth pattern. It appears often in deeper soft tissues, and is GLUT1 negative (31,32). Both KHE and TA may lead to severe consumptive coagulopathy and thrombocytopenia, also known as the Kasabach-Merrit phenomenon (30-34). Rare malignant vascular tumours include Kaposi sarcoma and angiosarcoma, which should be considered as differential diagnoses in non-typical cases.

Figure 4. Other vascular tumours: A. Pyogenic granuloma B. Kaposiform haemangioendothelioma C. Tufted angioma.



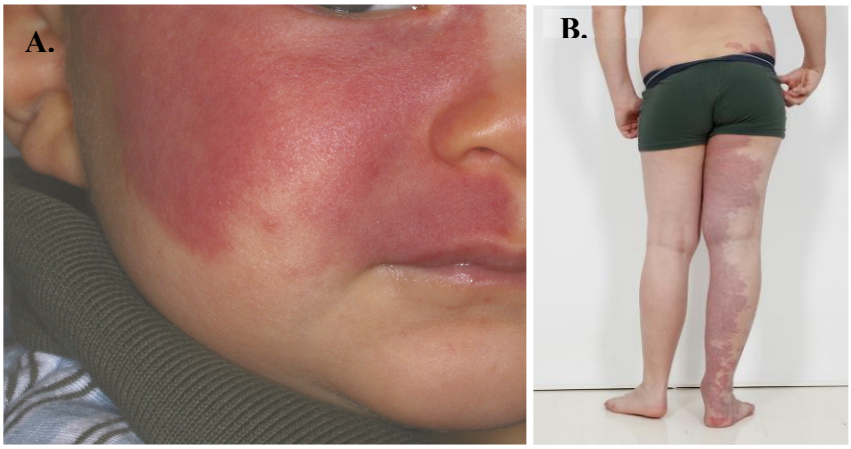
5.1.3. Vascular malformations

Vascular malformations comprise vascular lesions resulting from errors in vascular morphogenesis. They are present, but not necessarily visible, at birth; they grow according to their specific nature and almost never regress (1-3). Vascular malformations can be divided according to the vessel type they exhibit, as venous, capillary, lymphatic, or arteriovenous malformations, or according to the complexity of the lesion, as simple or combined malformations (Table 1). The rare group of malformations of major named vessels consist of vascular structures that involve major axial vessels, including also persistent embryonic vessels and congenital arteriovenous fistulas (1,5,18).

5.1.3.1. Simple vascular malformations

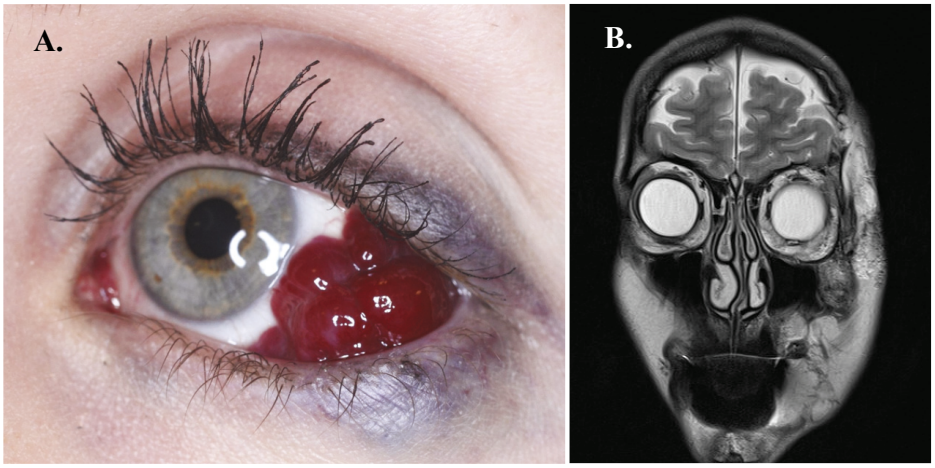
Capillary malformations (CM) are mostly benign and consist of morphologically anomalous capillary structures (Figure 5). They affect mostly skin or mucosa and are often called port-wine stains. CM has an estimated incidence of 0.3% (35). They are most often present at birth, normally persist throughout life, and may cause thickening or darkening of the skin, even though some lesions may also fade away over time. A small number of CMs are related to syndromes: CMs covering large areas of a limb may also involve other vascular malformations and soft tissue or bone overgrowth, i.e. in Klippel-Trenaunay or Parkes-Weber syndromes; large facial CMs may associate with Sturge-Weber syndrome (Table 1) (2,4,5).

Figure 5. A. Capillary malformation of the face. B. Capillary malformation associated with overgrowth of the lower limb.



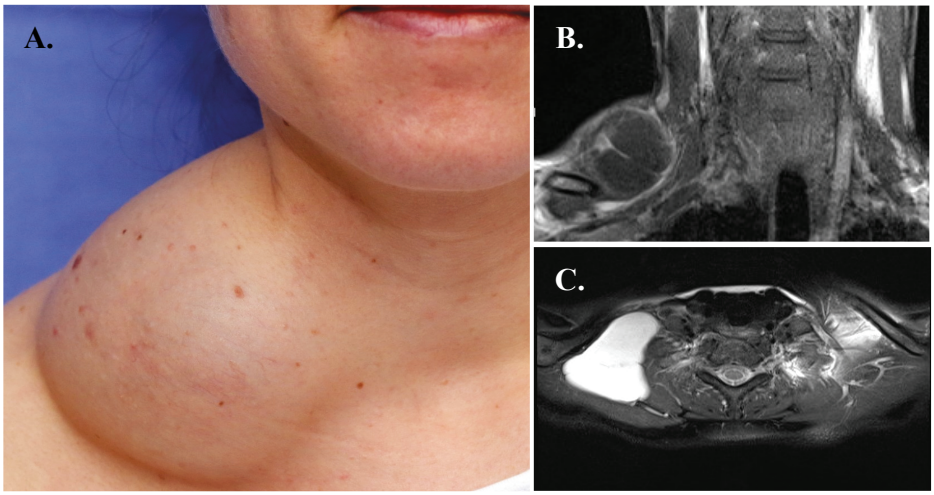
Venous malformations (VM) are low-flow lesions consisting of anomalous dilated veins that can affect any tissue or organ (Figure 6). They are the most common type of vascular malformations. Large VMs may result in local intravascular coagulopathy that may constitute major symptoms and cause treatment challenges (2,4,5). Venous malformations will be further discussed in section 5.3.

Figure 6. A large venous malformation (VM) in the sclera, extending into the orbit and cheek, A. An MRI of the same lesion, B.



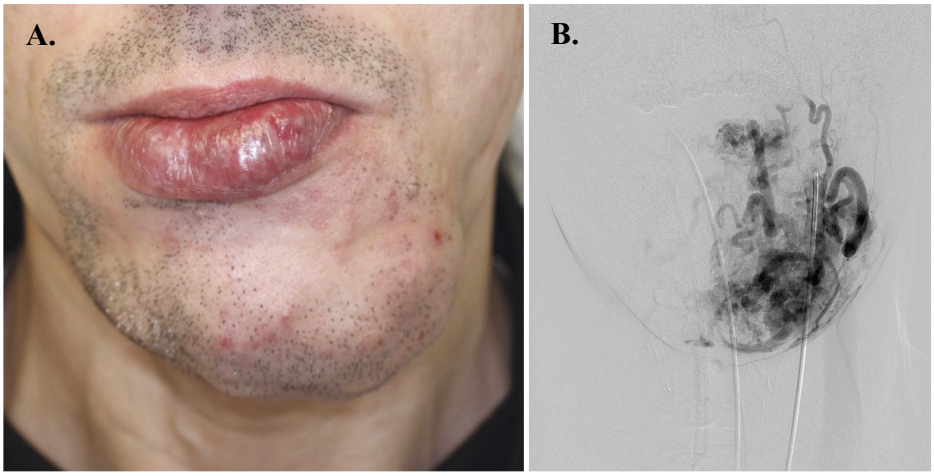
Lymphatic malformations (LM, Figure 7) are low-flow vascular malformations that comprise anomalous and differently dilated lymphatic channels filled with lymphatic fluid (4). They occur approximately at an incidence of 3 per 100 000 individuals (36,37). LMs can be further divided into macro-, or microcystic, or mixed lesions (1,4,38). Macrocystic LMs manifest as large fluid-filled cystic lesions, whereas microcystic lesions are comprised of several smaller cystic spaces. Approximately 75% of all LMs are located in the head and neck area and are usually diagnosed before the age of two (4,38,39).

Figure 7. A typical macrocystic lymphatic malformation of the neck, A., and a T1-weighted, B., and T2-weighted, C., MRI image of the same lesion.



Arteriovenous malformations (AVM) are high-flow vascular lesions and exhibit typically an aggressive growth behaviour (Figure 8). Their exact incidence and prevalence are as yet undefined (40). AVMs consist of morphologically anomalous arteries, veins, and capillaries in which arteriovenous shunting is present. They are pulsating, warm vascular lesions leading to ulcerations, bleeding, and potentially severe tissue disfigurement. AVMs often progress during pregnancy as the systemic blood volume increases. Due to the shunting and venous overload, AVMs, if left untreated, may result in cardiac compromise. Some AVMs are related to a mutation in the RASA1 gene (1,2,4,41).

Figure 8. An arteriovenous malformation (AVM) of the chin and base of the mouth, A. An angiograph shows the anomalous circulation in this lesion, B.



5.1.3.2. Combined vascular malformations

Combined vascular malformations may comprise combinations of any of these malformation types. The most common combined malformations are capillary-venous malformation (CM+VM), lymphatic-venous malformations (LM+VM), or capillary-lymphatic-venous malformations (CM+LM+VM). Combined vascular malformations may be associated with different syndromes (1,2,4,5).

5.1.3.3. Malformations associated with syndromes

A small number of vascular malformations involve also other anomalies as well, or are associated with syndromes that usually lead to deterioration in the patients' condition. These syndromes include Klippel-Trenauanay syndrome (limb overgrowth due to a combined malformation CM + VM +/- LM), shown in Figure 9, Parkes-Weber syndrome (limb overgrowth and a combined malformation, CM + AVF), Sturge-Weber syndrome (facial and leptomeningeal CM with ocular anomalies and possible bone or soft tissue overgrowth), and CLOVES syndrome (congenital, lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal or skeletal anomalies), and a number of other rare syndromes (Table 1). The distinctions, diagnostics, and management of these syndromes call for the expertise of an interdisciplinary vascular anomaly team (5,15,42).

Figure 9. A child with Klippel-Trenauanay syndrome.

5.2. Infantile Haemangioma

5.2.1. Definition

Infantile haemangioma is a benign vascular neoplasm that most commonly locates in the skin and subcutaneous tissue but may be found in any tissue or organ. It consists of proliferating endothelial cells that line the variable-sized blood vessels that form this vascular tumour. Peculiar to infantile haemangioma is its life cycle: it appears shortly after birth and may proliferate up to one year of age, after which it starts spontaneously to regress (1-3).

5.2.2. Epidemiology

Infantile haemangioma is the most common soft tissue tumour of childhood. Its incidence is estimated at between 2 and 10%; these estimates are based on different study populations and various study settings. IH is considered more common in Caucasian infants (1,4,6-9,43). A recent register-based study conducted in Minnesota estimated IH's incidence to be 2% (44). A Dutch study reported an IH prevalence of 9.9% (6). The incidence and prevalence of IH in the Finnish population is unclear. Karvonen and colleagues reported vascular birthmarks to appear at a frequency of 3.8% in infants aged 0 to 3 months, but this study did not differentiate IHs from other vascular lesions (45). IHs are more common in females: the male-to-female ratios vary from 1:1-3 (6,12). Other host-related risk factors include preterm birth and low birth weight, which is considered the strongest determinant (4,12,44,46). Prenatal and mother-related risk factors, shown in Table 2, include advanced maternal age, multiple gestations, *in vitro* fertilization therapy, placenta praevia, preeclampsia, transcervical chorionic villus sampling, and amniocentesis, even though reported risk factors vary depending on study setting and population (6,8,9,12,47-52). However, most of these risk factors relate to intrauterine hypoxia, which has been considered a major player in IH's pathogenesis (53). Familial clustering is one reported risk factor (12,54). Atopic disease has been positively associated with IH (55).

Table 2. Summary of risk factors for IH in earlier studies. Significant risk factors (**+**), and non-significant risk factors (**-**) for each study. Study settings are classified as prospective (P) or case-control (CC).

IH risk factors	P Munden et al. USA (n=29)	CC Rasul Uzbekistan (n=1832)	CC Chen et al. China (n=650)	CC Hoornweg et al. Netherlands (n=219)	P Dickinson et al. Australia (n=28)	P Haggstrom et al. USA (n=1058)
Host-related						
Female	-	-	+	+	+	+
Family history of IH	na	+	na	na	+	- *
Gestational						
Multiple pregnancy	na	+	+	na	-	+
Chorionic villus sampling	na	-	-	na	-	-
Amniocentesis	na	na	na	+	na	na
Placenta praevia	+	-	na	na	na	+
Preeclampsia	+	-	-	- **	na	+
Perinatal						
Preterm	+	-	+	na	+	+
Very preterm	+	na	na	na	na	+
Birth weight <2500g	+	-	+	+	+	+
Maternal						
Maternal age ≥35 years	-	-	-	na	na	+ ***
First childbirth	na	-	-	+	na	na
In vitro fertilization	na	-	+	na	+	na

Abbreviations: n: number of IH patients studied; na: not available; Preterm: <37 gestational weeks; Very preterm: < 32 gestational weeks or birth weight < 1500g. * First-degree relatives with haemangioma. ** Maternal hypertension. *** Maternal age ≥30.

5.2.3. Pathogenesis

IH pathogenesis has been under extensive study, but it is nevertheless only partly understood. The current consensus is that an IH derives from the embryonic-like progenitor cells that constitute the original source for endothelial cells in IH. These cells need an adequate cellular environment and external factors to develop an IH (56). The two main theories of the origin of these progenitor cells are these: that they are derived from circulating endothelial progenitor cells (EPC) or are derived from placental cells.

The EPC theory holds that an IH is a clonal tumour developed from intrinsic circulating endothelial progenitor cells that find an appropriate growth environment for vasculogenesis. The stimulus for EPC proliferation remains unclear: it may be hypoxia, a genetic factor, or a proliferation-prompting signal from surrounding tissues (57,58). This theory is reinforced by the finding of elevated levels of circulating EPCs in IH children undergoing surgical resection compared to age-matched controls (59,60). Moreover, research shows that IH-specimen-derived multipotential stem cells are capable of forming haemangioma in immunodeficient mice. These stem cells share characteristics with cord blood EPCs. EPCs are therefore suggested to be the origin of IH stem cells (61).

The placental theory, on the other hand, receives support from the finding that IH endothelium expresses many of the tissue markers expressed also in placental cells such as GLUT1 and other placental-specific markers (20,62-64). A recent study has revealed very similar expression between the proliferating endothelium of IH and placental chorionic villus mesenchymal core cells, hypothesizing that these cells are the origin of IH stem cells. The potential embolization of placental cells may either coincide with the first trimester's migration of neural crest cells along their somatic group, likely to result in segmental IH lesions, or be a result of embolization later in gestation, which may lead to focal or indeterminate IH lesions (65). The placental theory would also explain the higher incidence of chorionic villus sampling and amniocentesis in IH children's mothers, as these procedures can cause minimal disruption of placental cells and therefore promote the embolization (48,49,66).

Regardless of the origin of IH progenitor cells, they exhibit markers of primitive embryonic-like stem cells, thus giving further rise to the various cell groups of IH (61,67-71). The trigger for IH stem cells to proliferate and to differentiate is only understood in part: pro-angiogenic, pro-vasculogenic and anti-apoptotic factors may favour haemangiogenesis (56). Recent research emphasizes the role of the renin-angiotensin system (RAS) as the main regulator of haemangiogenesis: elevated renin levels result indirectly in high angiotensin II (ATII) levels that promote the cellular proliferation of IH (72,73). This effect is achieved by the capacity of ATII to activate vascular endothelial growth factor (VEGF) and anti-apoptotic osteoprotegrin (74,75). The VEGF-A isoform has been reported to play a crucial role in endothelial proliferation. It is highly sensitive to hypoxia and promotes angiogenesis and vasculogenesis (13,76-78).

To escape apoptosis, an up-regulation of the anti-apoptotic osteoprotegrin, a receptor for tumour necrosis factor-related pro-apoptotic ligand and a pro-tumour survival factor, has been observable in proliferating IHs. Logically, involuting IHs manifest reduced levels of osteoprotegrin, coinciding with the apoptosis of endothelial cells (79). Insulin-like growth factor 2 is reportedly expressed and produced by

proliferating endothelium of IH, most likely contributing as a growth factor, whereas reduced expression levels are apparent in involuting IHs (80,81).

The role of RAS as a crucial mediator in IH's pathogenesis coincides with the known IH risk factors: elevated levels of renin occur in females, in Caucasians, and in premature infants (74). Additionally, the physiological changes in renin levels during infancy also correspond well to the life-cycle of IH: up to 3 months of age, newborns exhibit five-fold serum levels of renin compared to those in adults, coinciding with the most rapid proliferation phase. Then, renin-levels decrease to three-fold at ages 3 to 12 months, coinciding with the late proliferative phase; to two-fold at 1 to 4 years, corresponding to the plateau and involution phase, and eventually from 8 years onwards renin levels decrease to adult levels (82). The importance of RAS as a crucial mediator is further supported by the current therapeutic approach for IHs: β-blockers reduce renin levels and therefore restrict IH proliferation (72,83). Additionally, captopril, an angiotensin-converting enzyme inhibitor, has been introduced into the treatment of IH (74,84). Comprehensive understanding of IH pathogenesis provides better tools for IH treatment.

5.2.4. Genetics

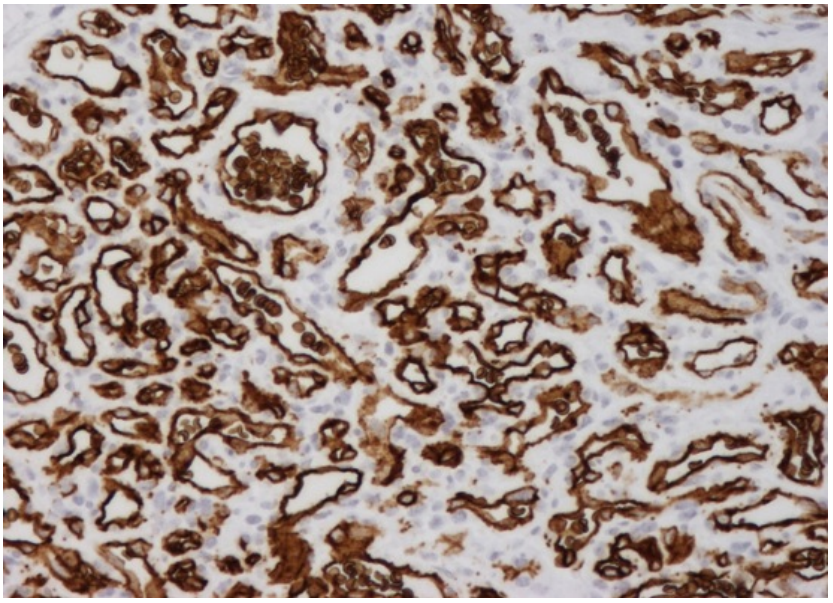
Despite extensive research, understanding of genetics in the development of IH remains limited. Most IHs occur sporadically, but familial clustering does occur, and family history of IH is regarded as a risk factor. Walter, Blei, and colleagues reported a subset of six families that showed an autosomal dominant IH inheritance pattern with high penetrance; in three of these families they showed a linkage to chromosome 5q31-33 (85,86). A population-database study in Utah reported a two-fold increase in relative risk for IH in siblings of an IH-affected proband, supporting familial predisposition as a risk factor (54). Children from multiple gestations have more IH; a recent prospective multicentre cohort study on 202 sets of twins showed, however, that concordance of IH between mono- and dizygotic twins was similar, and rather emphasized its multifactorial origin (87,88).

Mutations in genes regulating angiogenetic and vasculogenetic signalling pathways have been proposed as causative for IH in small patient cohorts: Jinnin and colleagues found germline missense mutations in proliferating haemangioma-derived endothelial cells in VEGFR2 and TEM8 genes, leading to inhibited integrin activity. They also speculated that a second event, either a somatic mutation or a physiological trigger, is necessary for IH progression (78). Walter and colleagues found missense mutations in single IH specimens in VEGFR2 and VEGFR3 (89). Clonality assays support a non-random X-chromosome inactivation in IH endothelial cells, suggesting a clonal origin for the tumour (57,89,90). The genetic variants - either somatic or germline - playing a role in IH pathogenesis in concordance with other physiological risk factors, remain as yet mostly unsolved (91).

5.2.5. Histopathology

The histology of IH varies dramatically depending on its stage. A proliferating IH consists of defined, unencapsulated capillary masses, aligned with endothelial cells and supporting pericytes. The cells reside in a multilaminated basement membrane with no association with smooth muscle cells. Mitotic activity is usually ample but benign. Due to the high-flow feature in proliferating IHs, yet mostly without arteriovenous shunting, enlarged and unorganized draining veins are often present. In contrast, involuting IHs exhibit few mitotic figures, apoptotic cell bodies accompanied by mast cells, and a reduced number of capillaries. These tissue structures are eventually replaced by fat cells (1,26,92). Characteristic of IH is the staining with GLUT1 antigen, a widely used immunohistochemical marker to distinguish IHs from other benign vascular tumours and malformations (Figure 10) (20). Of note, a rare verrucous haemangioma and some malignant tumours such as angiosarcoma also stain positive with GLUT1, emphasizing that the IH diagnosis should not only be based on GLUT1-positivity (20,93).

Figure 10. GLUT1-antigen-positive IH specimen.



5.2.6 Clinical presentations

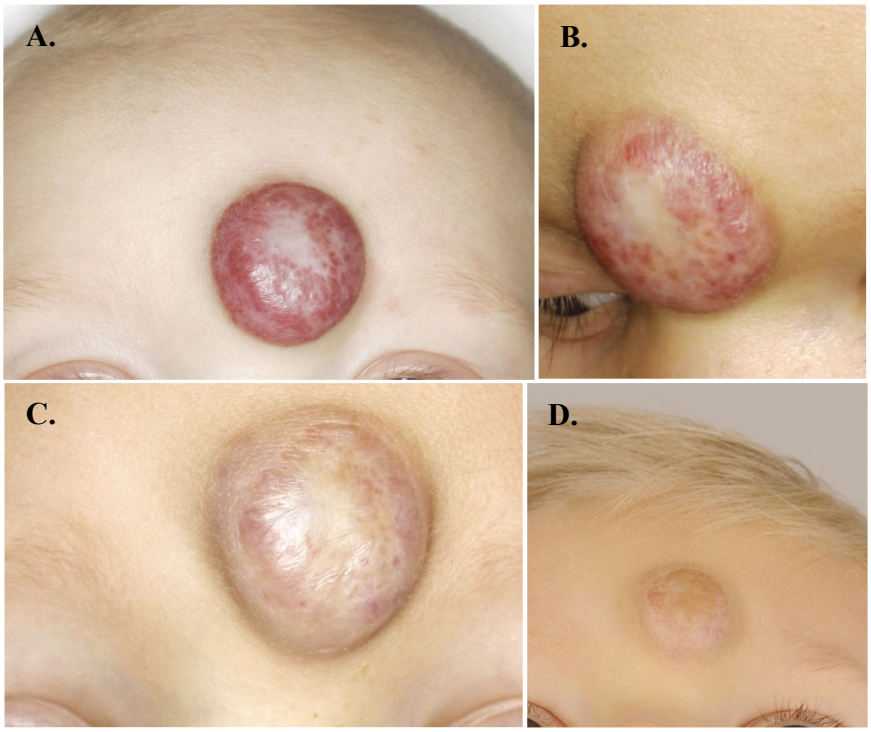
5.2.6.1. Clinical course

IH's clinical manifestation and typical life cycle make it relatively easy to distinguish IH from other vascular tumours and malformations. By definition, IHs are not present at birth; however, they may show blanching or local erythema that precedes their

initial onset (1,4). In early infancy, the IH starts its proliferation, during which it enlarges and reaches its typical configuration (94,95). Due to rapid proliferation, the surface of an IH may also ulcerate. The most rapid proliferation typically occurs early in infancy: 80% of IH growth is reached by 3 months of age, and by 5 months of age most IHs complete their growth (94). Superficial IHs tend to show an earlier onset of proliferation and growth completion, whereas deep IHs usually appear later and continue to grow longer. The proliferation phase of IH is typically completed by 12 months of age (4,96,97).

Between the proliferation and involution lies a plateau phase, during which proliferation and apoptosis are balanced (4,94,96,97). The involution phase usually begins at age 6 to 12 months, proceeds until age 10 to 12 years, yet major regression is usually reached by the age of 4. Involution often occurs by flattening of the IH from the centre outward (98-100). Despite their spontaneous involution, most IHs leave behind residual skin changes such as teleangiectasia, scarring, dyspigmentation, or fibrofatty tissue residue (Figure 11) (101).

Figure 11. Involution of a typical focal IH of the forehead. A. IH at age 6 months. B. At 1.5 years. C. At 2 years. D. At 5 years.



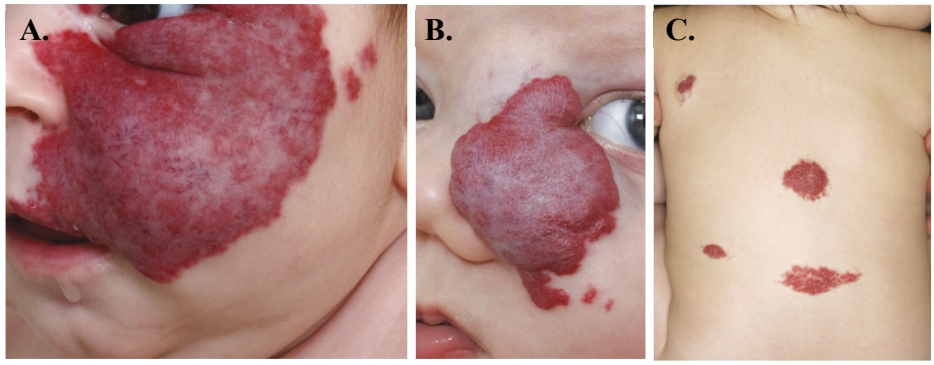
5.2.6.2. IH localisation and subtypes

Approximately 60% of IHs occur in the head and neck area. The second most common localization is the trunk, followed by limb manifestations (1,4). IH localisation is a major factor regarding each lesion's clinical importance and morbidity. Other major determinants are size, number of lesions, the soft-tissue depth, and the anatomic morphology (43,102).

Most IHs reside in the skin, and are categorized as cutaneous or superficial. They appear as red, "strawberry-like" lesions, with very little or no subcutaneous component. Superficial IHs usually follow an early-onset proliferation and involution pattern. Deep IHs, in contrast, reside subcutaneously, manifesting either a slight bluish surface or no surface coloration at all. Some IHs show both superficial and deep components and are therefore called mixed lesions (1,4,97,101).

IH morphological subtypes are classified as focal, multifocal, indeterminate, or segmental (Figure 12) (43,103-105). The focal subtype is the most common (60-70%), manifesting growth from a single focal point. Multifocal IHs, often classified as more than ten IH lesions, are rare but may associate with underlying hepatic haemangiomas (43). Five or more cutaneous lesions are considered as an indication for ultrasonography to check for hepatic IHs, as these may cause hepatomegaly and lead to congestive heart failure (106-108). The indeterminate subtype is the second most common, and occurs in approximately 17% of IHs: it shows clearly neither a focal nor segmental pattern (43).

Figure 12. IH morphological subtypes. A. Segmental IH. B. Indeterminate IH. C. A child with multifocal IHs, only those on back are shown.

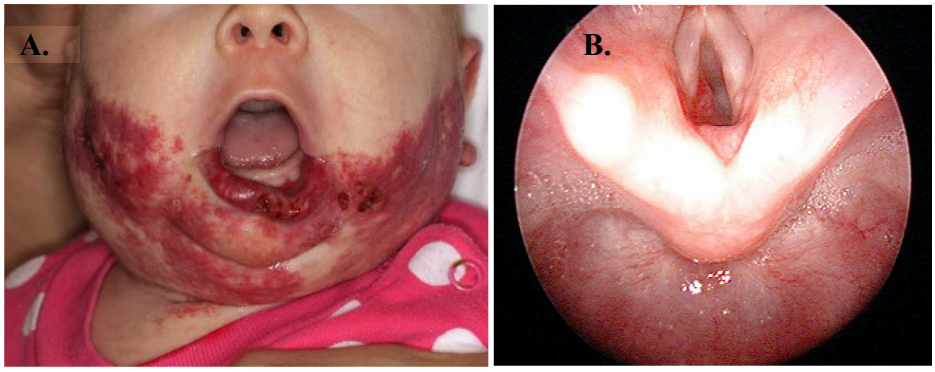


Segmental IHs follow a developmental dermatome, and they tend to invade large areas; they are relatively rare (13%) but often cause significant burden to the child, as they are more prone to complications. They may be associated with other anomalies

(43,102). In the face, segmental haemangiomas are further classified according to their developmental distribution as frontotemporal, maxillary, mandibular, or frontonasal (43,105).

Rarely, an IH may locate in the airways, especially in the supra- or subglottic area, causing inspiratory and expiratory stridor and potentially life-threatening airway obstruction during the first three months of life when proliferating (109-111). Children with an airway IH often manifest with a skin lesion: those with segmental IHs of the lower face in a "beard" distribution, especially bilaterally, covering the anterior neck, lower lip, and chin may have an underlying airway IH (Figure 13) (109-111). The exact incidence of airway IHs is unknown; Orlow and colleagues evaluated 529 children with IH, of whom 10 (2%) had an airway involvement, all of whom also manifested a cutaneous beard IH (109). When a child with a segmental facial or neck IH suffers from stridor, referral to an otorhinolaryngologist is therefore crucial to avoid delay in diagnosis of and treatment for any potential airway IH (112).

Figure 13. Infantile haemangioma with a beard distribution, A. The patient also had a subglottic IH causing airway obstruction, B.



5.2.6.3. IH complications

Despite the usual benign clinical course, an IH may cause complications. Earlier studies estimated that 20 to 40% of IH children suffer from any kind of IH complications (51,102). Of note, those studies have been conducted in a referral centre setting, probably exaggerating the rate compared to the complication rate in a primary health care setting. Major factors affecting complication risk are IH subtype, size, and location. The segmental subtype is regarded as the best predictor for a complication: segmental IHs are reportedly 11-fold more likely to result in complications, and eight-fold more likely to receive treatment than are non-segmental IHs. The larger the IH, the higher is the risk for complications and intervention. A

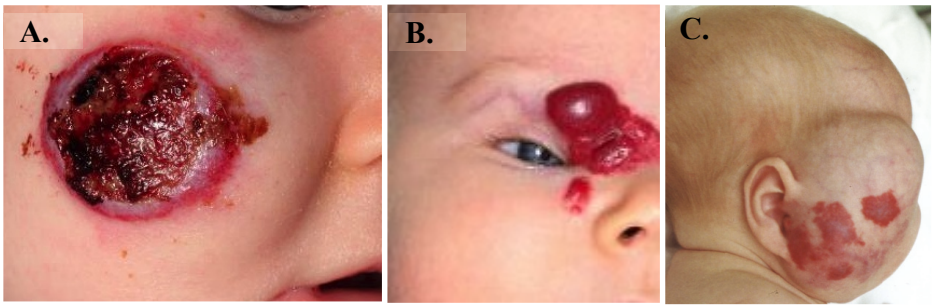
facial location bears a 1.7-fold complication risk compared to other locations, and it also predicts the need for intervention (102).

The most common IH complications are ulceration (5-21%), bleeding (up to 41%; severe bleedings are rare), and visual-axis compromise. Life-threatening complications such as cardiac compromise and airway obstructions are rare but possible (102,112). The nature of the complication often depends upon IH location and proliferation pattern. Predictors for IH complications are listed in Table 3. Figure 14 shows possible IH complications.

Table 3. Summary of IH complications (112).

Complication	**IH characteristic predicting complication**	**Complication mechanisms**	**Potential complication sequel**
Ulceration	Segmental, superficial subtype; Head, neck, perioral, perianal location	Tissue hypoxia, aggressive proliferation	Scarring, disfigurement
Bleeding	IH's ulceration	Surface trauma	Scarring
Visual impairment	Periocular, orbital or, nasal location	Ptosis, eyelid margin change, displacement of the globe	Amblyopia
Auditory canal obstruction	Periauricular and parotid gland location	Anatomic distortion, cartilaginous destruction	Conductive hearing impairment
Airway obstruction Nasal cavity obstruction	Airway IH, often present with "beard" IHs, nasal location	Proliferation of IH narrowing the airways, or nasal cavity	Life-threatening airway obstruction
Feeding obstruction	Lip or oral IH location	Ulceration or obstruction leading to painful eating or swallowing problems	Malnutrition
Cardiac compromise	Large size, aggressive IH proliferation, Multiple hepatic IHs	Arteriovenous shunting	Life-threatening cardiac insufficiency
Acquired hypothyroidism	Hepatic IH	Increased production of type 3 iodothyronine deiodinase	Growth retardation, neurological deficit

Figure 14. Complications of infantile haemangioma (IH). A. IH ulceration. B. Periorbital IH disturbing the visual axis. C. Massive IH of the parotid gland resulting in cardiac compromise and auditory canal obstruction.



5.2.6.4. IH-associated syndromes

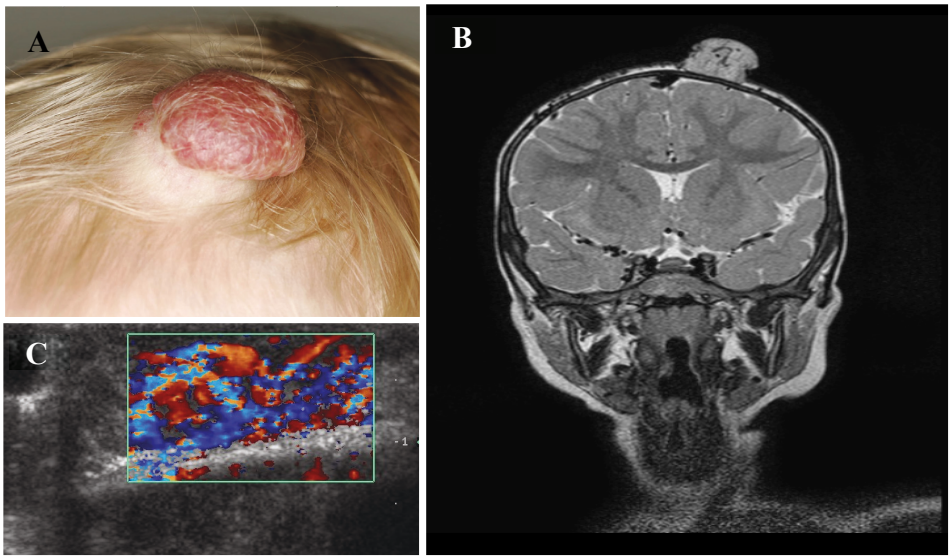
Even though rare, an IH may be a sign of an underlying syndrome that includes other congenital anomalies. Infants with a large facial IH (>5cm^2) should be monitored for PHACES (Posterior fossa malformations, haemangioma, arterial anomalies–cardiac defects, eye abnormalities, sternal cleft, and supraumbilical raphe) syndrome. PHACES syndrome involves defects in the cerebrovascular system in 90% of the cases, structural brain anomalies in 52%, and cardiovascular, mostly aortic, anomalies in 67%. Children with PHACES may also have ocular anomalies, and ventral or midline defects such as sternal cleft or supraumbilical raphe (102,113). Peculiar to PHACES is a segmental facial haemangioma of the frontotemporal or mandibular area. The pathogenesis of PHACES is unclear, even though earlier research has suspected the chromosomal region of 7q33 as being causative (114). All PHACES-derived defects can be explained by major developmental arterial vasculopathy, a possible key mechanism in PHACES pathogenesis (115). MRI imaging is indicated for children with large facial IHs to rule out this syndrome. In contrast to the typical IH risk factors mentioned, children with PHACES tend to be normal birth weight, full-term singleton infant (116).

Another congenital syndrome associated with IH is LUMBAR, which stands for lower body IH, urogenital anomalies and ulceration, myelopathy, bony deformities, anorectal malformations and arterial anomalies, and renal anomalies. LUMBAR is often regarded as a variant of PHACES, but in the lower body. LUMBAR-associated IHs usually manifest as segmental, readily ulcerating lesions in the lumbosacral or anogenital area. LUMBAR may involve underdevelopment of the affected lower limb. MRI imaging is indicated for children exhibiting this type of IHs to reveal potential extracutaneous manifestations of LUMBAR (117).

5.2.7. Diagnostic methods

The diagnosis for IH is usually clinical and is based on typical appearance and clinical course. Imaging studies serve for IH diagnosis when the clinical diagnosis is uncertain, when the extent of IH needs accurate evaluation, when associated extracutaneous anomalies are suspected, or when monitoring of the therapy response is important. Potential diagnostic imaging tools include MRI and ultrasonography (Figure 15). A biopsy is necessary only when the diagnosis is uncertain (5,112)

Figure 15. An IH on the scalp at age two years, A., MRI T2-weighted fat-saturated image of the same lesion, B., and circulation on Doppler ultrasound, C.

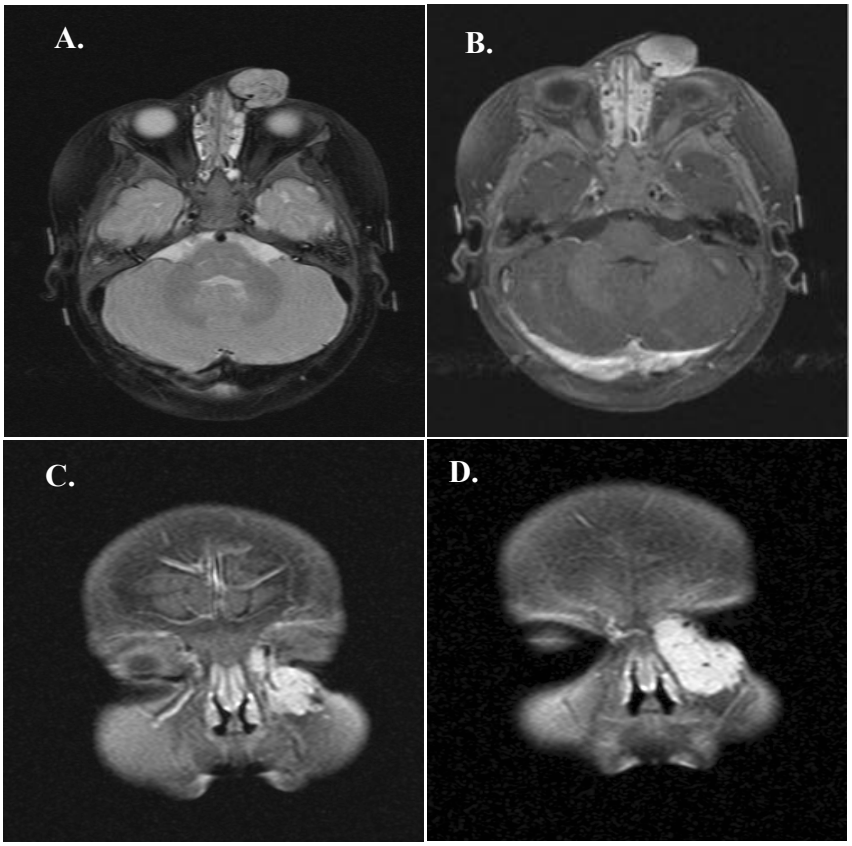


Ultrasonography (US) usually serves as an initial imaging modality, because it lacks ionizing radiation and requires no sedation. Depending on the IH's proliferation phase, US findings include a well-defined soft-tissue mass with high-flow circulation and possible shunting, but later in the involution phase, areas of fat replacement are often present. US can also serve as a primary screening method for children with multifocal IHs that may have liver or visceral manifestations, although MRI is preferred for more complex cases (118).

When the full extent of IH and its potential extracutaneous manifestations necessitate visualising, MRI serves as a primary diagnostic tool (Figure 16). The need for anaesthesia and its potential to damage a developing brain is, however, a major MRI drawback (119,120). On MRI, proliferating IHs manifest as well-defined high-flow masses and show some signal intensity on T1-weighted images and strong signal

intensity on T2-weighted images (121,122). When gadolinium is administered as a contrast medium, IHs usually exhibit enhancement and filling on early images (123).

Figure 16. A typical MRI finding of a periorbital IH. A. Axial T2 fat-saturated image. B. Axial T1 fat-saturated image with gadolinium. C. and D. Coronal image T1 fat-saturated with gadolinium.



When the diagnosis remains unclear despite clinical examination and imaging studies, or when other vascular tumours or malignant conditions must be ruled out, biopsy and histopathological examination is necessary (5,112).

5.2.8. Treatment

Due to IHs' spontaneous regression, most lesions do not require treatment. Nevertheless, estimates show that approximately one-third of IHs need some kind of intervention, even though tertiary-centre study settings and referral bias may exaggerate these estimates (6,102). The commonly accepted indications for intervention include a potentially life-threatening complication, functional impairment, pain, and bleeding, and reduction in potential long-term disfigurement. For lesions with a low complication risk, watchful waiting is usually sufficient (112). The choice of treatment modality depends on patient age, growth phase of the lesion, IH location and size, degree of skin and tissue involvement, complication severity, and urgency of the intervention, possible future consequences, parental preference, and physician's experience (112). Therapeutic approaches can be divided into three categories: local, pharmacological, or operative therapy, or combination of these. Since the introduction of propranolol, a non-selective β-blocker, this has been the first-line therapy for all IHs necessitating systemic therapy (124-126).

5.2.8.1. Local treatment

Local treatment is usually necessary for superficial cutaneous IH lesions that tend to ulcerate. Careful wound care is the basis and it usually consists of barrier dressing of the lesion to avoid trauma, secondary infection, excessive drying, and pain. Topical antimicrobial products and analgesics often serve as adjuvant treatment (112,127).

5.2.8.2. Pharmacological treatment

Local or systemic corticosteroids have been the first-line pharmacological treatment for IH, but due to their side-effects and the introduction of β-blockers for IHs, they are now less frequent (128,129) (Table 4). Oral propranolol is currently considered as the first-line systemic therapy for IHs (124,125,130,131). Current research suggests that propranolol effectively limits IH proliferation by causing vasoconstriction, inhibiting angiogenesis and nitric oxide production, and reducing renin levels, therefore limiting IH proliferation (56,83,132,133). Systemic β-blocker therapy is indicated for ulcerating IH, for impairment of vital functions, or for IH at risk for causing permanent disfigurement. Contraindications include cardiogenic shock or heart failure, sinus bradycardia, greater than first-degree AV-Block, hypotension, bronchial asthma, or hypersensitivity to the product (130). Propranolol has proven safe and efficient: a recent randomized controlled multicentre trial compared placebo to oral propranolol of 1 and 3 mg per kilogram/day during 3 to 6 months for 456 infants (126). The study found the 3-mg daily dose to be safe and efficient compared to placebo, with adverse events such as bradycardia, hypotension, bronchospasm, and hypoglycaemia being relatively infrequent. Another concern raised for propranolol's use is its lipophilic nature and capacity to pass the blood-brain barrier, which may cause neurological side-effects such as sleeping disturbances (131). To date, no evidence exists on any long-lasting cognitive deficit on children having received propranolol therapy (134).

Other β-blockers have also been introduced into the management of IH. Oral atenolol has been proposed as an alternative for propranolol, because it is a hydrophilic selective β1-blocker and has less frequent adverse events; larger studies on its safety and efficacy are lacking, however (135-137). Topical timolol has also been suggested as an alternative for propranolol for superficial IH's but it bears the risk of less controlled topical dosing but similar adverse effects as from other β-blockers (138,139).

Earlier, vincristine and interferon-α were occasionally used for difficult IHs, but due to their neurotoxic and other difficult side-effects and the introduction of β-blockers, they are virtually no longer in use (140-142). Captopril, an angiotensin-converting enzyme inhibitor, has also recently been introduced in IH treatment, as it is able to inhibit the RAS (74,84). Investigators have also proposed that anti-angiogenic agents based on VEGF inhibition may restrict IH proliferation (143). Rapamycin, an mTor-inhibitor, has proven to be efficient against other vascular malformations and has also shown some efficacy against IH (144).

Table 4. Summary of the most common medical therapies for infantile haemangioma, their indications and side-effects.

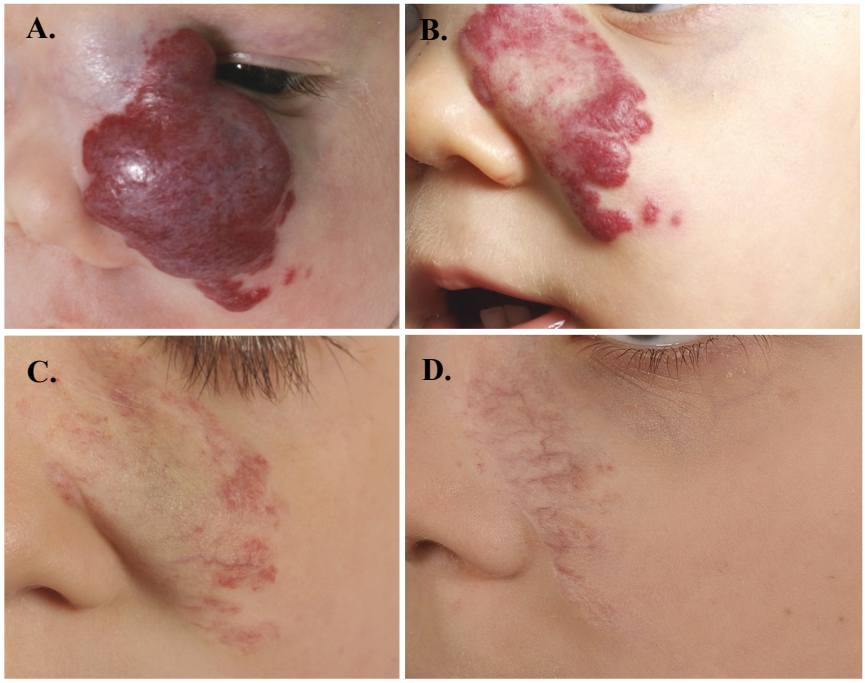
Pharmacological agent	**Indications**	**Side-effects**
Systemic β-blockers (propranolol, atenolol)	IH necessitating systemic therapy	Bradycardia, hypotension, hypoglycaemia, diarrhoea, cool extremities, sleep disturbances
Topical β-blockers (timolol)	Superficial IH	Same as above
Captopril	IH necessitating systemic therapy	Renal insufficiency Hypotension
Systemic corticosteroids	IH necessitating systemic therapy when β-blockers are contraindicated or have not been efficient	HPA axis suppression, cushingoid features, growth restriction, weight gain, hypertension, gastric irritation, irritability, insomnia, immune suppression, cardio- and steroid myopathy, osteopenia, ocular effects
Intralesional corticosteroids	Small, localised IH	Fat and dermal atrophy, hypopigmentation, same as with systemic corticosteroids

Abbreviations: HPA axis: Hypopituitary adrenal cortex axis.

5.2.8.3. Laser therapy

Before the introduction of β -blockers, pulsed-dye laser (PDL) therapy has been widely in use for superficial IHs. Nowadays, PDL mostly plays an adjuvant role in IH treatment (112). PDL tissue penetration of 2 mm limits its use only to the superficial IH component. The results and efficacy of PDL for IH are somewhat controversial (145-147); however, PDL may be efficient for early superficial facial IHs, for the superficial component of a mixed-type IH, for IHs with refractory ulceration, or for residual teleangiectasia (146,148). The requirement of anaesthesia limits the use of laser therapy, even though very small lesions can be treated under local anaesthesia (112).

Figure 17. An infantile haemangioma causing visual compromise and nasal-cavity obstruction. A. At age 3 months before initiation of therapy. B. At age one after systemic corticosteroid therapy. At age 5 years C. and at age 7 years D. after laser therapy and surgical correction.



5.2.8.4. Surgical treatment

Prior to the development of medical and laser therapy, surgery was, in addition to corticosteroids, one of the few IH-treatment options. Despite β-blockers, surgery still has a place in some IH treatment, especially for scar corrections due to tissue residue from an involuted IH around the age of three to six years (4,161). Surgery for IH as a

primary treatment is indicated in cases with failure or contraindication for medical treatment, or for complicated but focal IHs in an area favourable to surgery (4,149). Nonetheless, the risks of surgery, including potential blood loss, iatrogenic injury, and need for anaesthesia at a very young age limit its use.

5.2.9. Prognosis

The course of IH is generally benign, and most IHs resolve without intervention and leave no permanent sequel. However, although one referral centre study estimated that approximately one-third of IH children needed some kind of intervention, recent prospective studies in primary health care settings estimated that only 4% of IHs necessitated intervention (8,9,102). Only a few investigations have measured the long-term morbidity and quality of life in IH children. In young IH children, head and neck IHs and history of intervention have been linked to elevated morbidity levels (150). Earlier studies in small patient cohorts report that the quality of life for older IH children was generally similar to that of age-standardised quality-of-life levels (151,152). How propranolol treatment changes the long-term outcomes for IH patients, remains as yet unreported.

5.3. Venous Malformations

5.3.1. Definition

Venous malformations result from congenital errors in the vascular morphogenesis involving venous structures. VMs comprise dilated disorganised venous channels that may invade any tissue or organ. The size, invasion and growth characteristics of VM are highly variable (1-3).

5.3.2. Epidemiology

VMs are the most common type of all vascular malformations, and are the second most common among all vascular anomalies after IH (1,4). Due to diagnostic challenges and the natural course of VM, its incidence and prevalence rates are unclear. Estimates of its incidence are 1 to 2 in 10 000 births, with a prevalence of approximately 1% (4,11,153,154). VMs occur approximately as often across genders (42). Other host-related risk factors are unknown, because the pathophysiology relies mostly on genetic predisposition (153).

5.3.3. Pathogenesis

Defects in vascular morphogenesis lead to the formation of a venous malformation (1,4). The PI3K/AKT signalling cascade, responsible for vessel stability between endothelial cells and supporting cell groups, plays a crucial role in the pathogenesis of venous malformations, and alterations or dysfunction in this cascade result in the formation of a VM as well as in some other vascular malformations (91,155-158). Vikkula and colleagues made a breakthrough discovery in finding one causative mutation for VM: a mutation in the TEK gene that encodes the tyrosine kinase receptor TIE-2 causes approximately 60% of the sporadic VMs (158,159). The TIE-2 receptor binds angiopoietins that regulate vasculogenesis and angiogenesis: they alter endothelial cell proliferation, migration, and adhesion, maintain vessel stability between endothelial cells and their supporting cells, and maintain vascular quiescence (155,158,160). Thanks to these functions, the TIE-2 receptor regulates the PI3K/AKT signalling cascade. Mutated forms of the TIE-2 receptor activate this cascade in a ligand-independent manner, resulting in diminished levels of the platelet-derived growth factor needed to recruit mural cells to support the endothelium. This leads to vessel instability and discordance between endothelial cells, pericytes, and smooth muscle cells, and allows uncontrolled vessel sprouting. Dysfunction in this signalling cascade therefore contributes to VMs' continuous dysmorphogenesis (91,155,157,158,161).

5.3.4. Genetics

Most VMs occur sporadically (94%), supporting the theory of a somatic mutation Four genetically different types of VMs exist, two of which are sporadic and two inherited. Sporadically occurring VM includes the classic venous malformation and

the rare blue rubber bleb nevus syndrome. The inherited forms of VMs comprise cutaneomucosal venous malformations and glomuvenous malformation (41) .

The genetic cause for the classic sporadic VM has been identified as involving mutations in the TEK gene encoding the TIE-2 receptor in approximately 60% of cases, and in about 20% of cases mutations in the PIK3CA gene; these are both crucial players in the PI3K/AKT signalling pathway. The mutations occurring in sporadic cases have never been observable in inherited cases, suggesting that they are lethal during embryogenesis (155,156,158,160,162). Another sporadic VM type manifests as the blue rubber bleb nevus syndrome. It is rare and is characterised by several cutaneous and intestinal VM lesions, often leading to chronic anemia due to bleeding (41,163). For the blue rubber bleb nevus syndrome, a specific somatic TIE2 mutation form has recently been considered causative (164).

Inherited forms of VMs account only for approximately 1 to 5% of all VMs. They include the autosomal dominantly inherited cutaneomucosal venous malformations caused by gain-of-function mutations in TIE2, distinct from the mutation that is observable in the sporadic form (156,160,161). Another type of an inherited VM is called a glomuvenous malformation: this also follows an autosomal dominant inheritance pattern. Glomuvenous malformations are clinically quite similar to sporadic VM, but they have some peculiar features: they appear as pink or bluish lesions, mostly superficially and often elevated on the skin (165). Glomuvenous malformations result from mutations in the glomulin gene that affects angiogenesis and smooth-muscle cell development (166-168).

Understanding of genetic mutations that alter the function of the PI3K/AKT signalling cascade at various stages has led to dramatically increased understanding of the pathophysiology of VM types, and for VMs has facilitated the development of targeted medical therapies (169).

5.3.5. Histopathology

Venous malformations appear as dilated or thickened dysplastic vascular channels lined with mature endothelial cells with no internal elastic lamina and only a partial smooth muscle cell lining (1,92). Erythrocytes are observable in the vascular spaces, and due to the VM-related local intravascular coagulopathy, luminal thrombi and calcified phlebolitis are often present. To differentiate VMs from LMs, many fewer intraluminal erythrocytes occur in LMs, as LMs contain mostly lymphatic fluid. AVMs, on the other hand, can be distinguished from VMs thanks to AVMs' characteristic dilated arterial structures, thick walled veins, and disturbed vessel architecture (92,170).

Immunohistochemical staining is in all vascular malformations quite similar. Unlike the IH, vascular malformations stain negative with GLUT-1 marker (92). All vascular malformations seem to stain positive with nerve-tissue-avid S-100 stain (171). VMs

and LMs may, however, microscopically resemble each other. For the distinction, D2-40 antibody stains positive in LMs but negative in VMs (172).

5.3.6. Clinical presentations

Venous malformations appear as variably-sized abnormal veins that may invade any tissue or organ. VMs may appear as either superficial or deep and can be either diffuse or localised (Figure 18). Some patients suffer from multiple lesions. VMs are typically soft, non-pulsating, bluish lesions that often accentuate and become apparent in a dependant position, during the Valsalva manoeuvre, or at physical exercise. Due to the slow-flow nature, coagulation and painful phlebolitis may occur.

Figure 18. A. A venous malformation (VM) of the lip. B. A VM in the ear lobe.

5.3.6.1. Clinical course

VMs are present but often not visible at birth, progress slowly commensurate with physiological growth, and never regress. Trauma, partial resection, puberty and pregnancy often accelerate VM growth due to the increase in blood volume and to probable hormonal factors (1,4,92,173,174).

5.3.6.2. VM localisation and tissue involvement

Approximately 40% of the VMs reside in the head and neck, most commonly in the cheek, lip, or oral cavity. Extremity VMs account for 40% and trunk VMs for 20% of all VM lesions. VMs vary in size and tissue infiltration, potentially invading any tissue plane, joint, or the viscera (Figure 19) (173,174).

Figure 19. A. A venous malformation behind the tonsil that extends diffusely to the neck, manifesting as bluish skin in the neck, B.

5.3.6.3. VM symptoms and complications

VM symptoms are highly dependent on lesion size and location. Most typical VM symptoms include pain and swelling due to position or physical activity, aesthetical discomfort, functional impairment, local compression of neural, capsular, or fascial structures resulting in pain, and restricted joint or muscle movement (4,173). Due to the slow-flow nature and stasis in the VM, chronic localized intravascular coagulopathy is often present, leading to thrombosis but also to bleedings due to low fibrinogen levels. This coagulopathy predisposes patients to severe thromboembolic complications, such as pulmonary embolism, but also to bleedings due to consumption coagulopathy (170,173). VMs infiltrating the orbit often cause visual impairment, and VMs near the airways may lead to airway obstruction (4).

5.3.6.4. VM-associated syndromes

Some VMs are related to syndromes that usually aggravate the clinical presentation (5). Klippel and Trenaunay described in 1900 a syndrome with a distorted and hypertrophic lower limb affected by a diffuse VM, combined with a capillary-, or a lymphatic component, or both (4). Klippel-Trenaunay syndrome manifests mostly unilaterally in one limb, although bilateral cases do occur. Symptoms and morbidity of this syndrome involve cutaneous staining due to the capillary component, lymphedema and cellulitis due to the LM, and venous structural abnormalities affecting both the superficial and deep venous system, leading to valvular incompetence, dilations, and venous stasis. These may result in ulceration, coagulopathy, deep venous thrombosis, and potentially to pulmonary embolism (4,175-177). Most cases occur sporadically; gene mutations in pro-angiogenic factors or proteins in the PI3K/AKT signalling pathway have been proposed as causative (41).

In addition to Klippel-Trenaynay, there occurs a set of other syndromes involving VMs. Inherited forms of VMs have already been discussed. Mafucci's syndromes comprise venous and lymphatic malformations accompanied by multiple enchondromas, exostoses, and spindle cell haemangioendotheliomas. Proteus syndrome involves mixed vascular malformations with skin disorders, overgrowth, atypical bone development, and high tumour incidence. Gorham-Stout syndrome associates with venous or lymphatic malformations or both, and results in bone loss replaced with fibrous tissues. Bockenheimer syndrome is a rare, congenital, progressive diffuse phlebectasia affecting most commonly the upper limbs (177-179).

5.3.7. Diagnostic methods

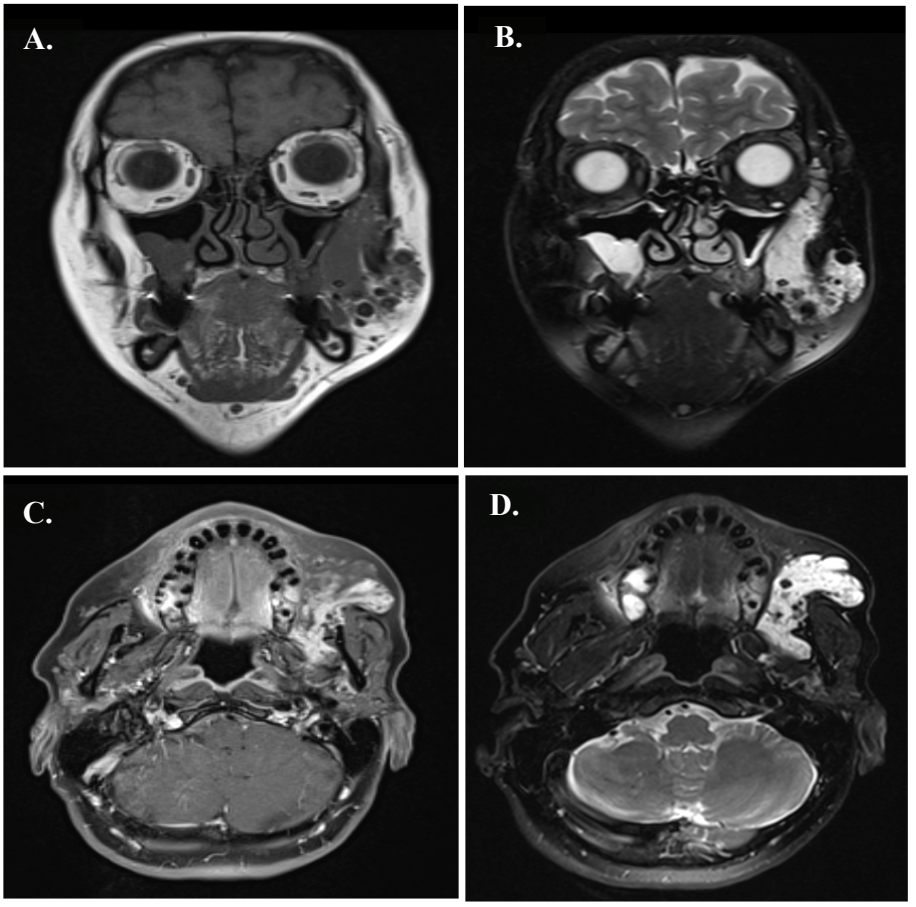
The diagnosis of venous malformations is based on typical clinical course and presentation, imaging studies, and on histopathology, when diagnosis is uncertain (180-182). Correct diagnosis is often difficult: based on a large vascular-anomaly-centre study, the referral diagnosis for a VM patient was correct only in 31% of the cases, emphasising the importance of an interdisciplinary vascular-anomaly team. Distinguishing VMs from AVMs and other vascular malformations as well as from vascular tumours and malignant lesions is crucial. Medical photography serves as a useful tool in the follow-up (15,42,182).

Ultrasonography (US) usually serves as first-line imaging for VMs, as it is widely available, non-invasive, devoid of ionizing radiation, and applicable without general anaesthesia. In addition, it plays an assistive role in image-guided biopsy or intervention (180,183). US serves for relatively superficial and confined lesions, but with US, deeper and more diffuse lesions are difficult to completely visualize with US (154). VMs usually appear in US as heterogenous and hypoechoic. Their vascular spaces may contain phlebolitis, which is pathognomonic for VMs (173,184). When the diagnostic probability for a vascular malformation is high, a US examination can usually clarify the flow of the lesions, in order to distinguish high-flow lesions (AVMs) from low-flow lesions (VM and LM) thanks to Doppler analysis (184). In cases with any diagnostic doubt as to lesions other than a vascular malformation, other imaging modalities or biopsies are necessary (180,185).

MRI has become the first-line imaging choice for VMs when US and clinical examination are insufficient (Figure 20). The advantages of MRI include a non-invasive and non-radiating evaluation of the whole lesion architecture and adjacent structures as well as excellent soft-tissue- and flow assessment. MRI is usually applied when planning an intervention. The disadvantages of MRI are the necessity of anaesthesia in paediatric patients, higher cost, and lower availability than with US (173,181,186,187). On T1-weighted images, VMs appear as iso- or hypointense, and occasionally hyperintense when containing fat. On T2-weighted images, VMs show high signal intensity. Gadolinium in fat-saturated sequences reveals the lesion's vascularity and thus distinguishes it from perilesional fat (121,173,181,187-190). On MRI, VMs differ from AVMs in T1 and T2 signal intensities, and in the amount of

soft tissue component, scarce in AVMs (121,174,186,187,191). Dynamic contrast-enhanced MR-angio- or venographic techniques help in distinguishing between high and low-flow lesions (192-195). The distinction between VM and LM is usually clear, as the latter is not enhanced with gadolinium, although microcystic LMs may, in MRI, mimic VMs (121,174,187,196). MRI combined with dynamic techniques provides 100% sensitivity and 95% diagnostic specificity (192).

Figure 20. A typical venous malfromation with phlebolitis in T1 sequence: A. in T2 fat-saturated image, B. and D., and C. coronal T1 image with gadolinium.



Phlebography, usually performed under fluoroscopy as a direct percutaneous puncture of the VM and then contrast injection, serves for assessing VM morphology and flow characteristics. It is often used prior to sclerotherapy (173,181).

When any uncertainty exists as to VM diagnosis, a biopsy and histopathological examination is necessary to rule out malignancies. Unlike malignant lesions, VMs exhibit flat, mature endothelial cells. To distinguish VMs from vascular tumours and other vascular malformations requires immunohistochemical staining (1,92).

5.3.8. Treatment

Treatment of VMs constitutes a challenge. As in treating any non-malignant disease, careful assessment of treatment indications and of possible treatment-related complication risks will prove crucial. When the VM causes haemorrhage or severe coagulopathy, or threatens vital structures or functions, intervention is necessary. Relative indications for intervention include pain, discomfort, and functional or aesthetic impairment. The decision on intervention for VMs and the treatment strategy should be tailored to each patient individually in an interdisciplinary setting (173,197).

5.3.8.1. Conservative treatment

A number of VM patients can be conservatively managed after proper diagnostics and patient information in case the VM symptoms are bearable (4,173,174). The first conservative treatment option is a compressive garment or stockings, especially for extremity VMs. These garments aim to limit tissue swelling and pain, to slow the progression of the VM, to alleviate the localized intravascular coagulopathy, and to reduce the risk for thrombosis. When marked localized intravascular coagulopathy occurs with elevated D-dimer and low fibrinogen levels, anticoagulation is indicated to reduce the risk for thrombosis and thromboembolic complications as well as to alleviate the pain due to existing thrombosis (170,173,188,197,198).

5.3.8.2. Surgical treatment

Before the development of modern interventional radiology, surgery was virtually the only intervention modality for VMs (4). Even though interventional radiological techniques have gained ground, surgery is still an appropriate treatment modality for some lesions. Focal, confined VMs, for which complete excision is possible without loss of significant adjacent tissues, are suitable for surgery (173,197,199). Nowadays, surgery serves mostly as an adjuvant treatment after sclerotherapy or laser therapy for large VMs in which a sufficient number of venous channels must be closed with intravascular techniques before tissue excision (4,199). The disadvantage of surgery is the loss of large tissue areas and, when only partial resection is achieved, re-growth of the VM (173,182,197).

5.3.8.3. Percutaneous sclerotherapy

Percutaneous sclerotherapy is considered as the first-line therapy for most VMs. The goal of sclerotherapy is to damage endothelial cells within the VM, resulting in scarring and closure of the vascular channels and eventually in shrinkage of the VM. The aim of sclerotherapy is symptom relief. For large lesions, sclerotherapy also targets control of coagulopathy and aims to facilitate further surgery by reducing the

volume of open vascular spaces (4,154,173,174,197). Successful and complication-free sclerotherapy is dependent on the sclerosant agent, patient preparation, and the technical expertise of the interventional radiologist (197,200,201).

Sclerosing agents

The choice of sclerosing agents depends on VM location and morphology. Sclerosing agents differ in toxicity, viscosity, and complication risks. Currently many agents, either alone or in combination, can achieve the best possible result with an acceptable risk profile (Table 5). Due to the heterogenous study settings, however, no clear evidence yet exists as to the superiority of any one sclerosant (202,203). To treat VMs in confined areas, sclerosants causing the least oedema, ones such as bleomycin, may be wise choices. Sclerosing agents are listed in Table 5.

Table 5. Summary of sclerosing agents (182,202-210).

Sclerosing agent	Advantages	Disadvantages
Ethanol-based sclerosants		
Ethanol (95%)	Effective Recanalization rare Inexpensive	Potentially very toxic Local complications: tissue necrosis, nerve injuries Systemic complications: haemoglobinuria, pulmonary hypertension and embolism, cardiac collapse
Ethanolamine oleate	Viscose, low vessel penetration Safer than ethanol	Systemic complications: haemolysis, renal insufficiency, hepatotoxicity
Ethanol Gel	Viscose, low vessel penetration Safer than ethanol	Local tissue injuries Fewer systemic side-effects than with ethanol
Detergent sclerosants		
Sodium tetradecyl sulphate (STS) 3%	Detergent, foam allows good endothelial contact	More recanalization Local complications possible Systemic complications: urticaria, anaphylaxis, haematuria
Polidocanol	Detergent Painless In different concentrations	Local complications possible Systemic complications: Haemolysis, haemoglobinuria, cardiac arrest (rare)
Sodium morrhuate	See STS	Less effective than STS
Others		
Bleomycin, Pingyamycin	Anti-cancerous antibiotic Minimal swelling	Transient fever, skin necrosis, tissue atrophy, potential pulmonary fibrosis

Sclerotherapy procedure

Monitoring the patient's coagulation status is advisable. Sclerotherapy is mainly executed under general anaesthesia; only small and superficial VMs, along with sufficient patient co-operation, are suitable for treatment under local anaesthesia (182). The patient should be informed of the course and possible complications of sclerotherapy.

Prior to injection of the sclerosant, assessment of the VM morphology and drainage is necessary. This is usually achieved by phlebography or by iodinated contrast injection under US-guided fluoroscopy (182). If the venous drainage flows into large or critical veins, mechanical compression is necessary to prevent any systemic leak. Currently, the draining technique is widely used: several needles are placed into the VM, and after confirming their entry into the venous space by retrograde blood flow, the sclerosing agent is injected through one needle, while other needles permit the sclerosant outflow. This technique prevents VM's overfill, any rise in intraluminal pressure, and any potential sclerosant leakage (211).

Patients are monitored after sclerotherapy depending on VM extent and location: patients with small lesions can be discharged after two to three hours of monitoring, whereas patients with large VMs located close to critical structures or with any coagulation disturbance should be hospitalized until stable (182,201,212). After the procedure, a compressive garment helps to reduce swelling and supports closure of the venous channels. When extensive oedema is expected, per oral corticosteroid administration is advisable for 3 to 5 days. Regular analgesics serve for pain relief. Follow-up and consecutive therapies are programmed for each patient individually depending on response to the therapy (182,201,209,212).

Sclerotherapy outcome

Sclerotherapy outcome depends on patient satisfaction, symptom relief, and clinical evaluation. Objective and standardized outcome- and complication-measurements methods for sclerotherapy are lacking, mostly due to the heterogeneity of VMs, differing practices between vascular-anomaly centres, and variable study settings. Recent review studies could find no superiority of any sclerosants in regards to sclerotherapy outcome; in one review, the complete-response rate (regression of at least 80% of the vascular malformation) ranged from 33% to 76%, and overall response (subjective symptom relief or reduction in VM volume) rate was 71% to 100%. Another review study stated that among ethanol, polidocanol, ethanolamine oleate, and STS, all but STS exceeded a total efficacy rate of 90%. However, follow-up periods in the studies included in the reviews ranged from 0 to 120 months, mostly being between 3 and 20 months, rendering evaluation of long-term efficacy difficult. Additionally, the academic quality of these studies was evaluated as being low or very low (202,203). Based on the current literature, solid and objective evaluation of sclerotherapy efficiency and of various sclerosants is therefore difficult.

Sclerotherapy complications

Currently no standardized consensus exists on classifying sclerotherapy complications. However, because sclerotherapy has largely replaced surgery in VM treatment, systematic assessment of complications is necessary. Most studies divide complications into local and systemic, or minor and major complications, leaving the interpretation subjective (203). The Society of Interventional Radiology has introduced a classification for all radiological procedures, but this is only in part applicable in sclerotherapy, as it divides complications into minor and major complications, and therefore remains relatively subjective (213). An alternative classification for sclerotherapy could be the Clavien-Dindo classification of complications, widely applied and standardized in surgery (214-216). It divides complications into five categories dependent on the procedures needed to treat the complication, which makes it an objective grading system. The weakness of the Clavien-Dindo classification is, however, that complications leaving permanent nerve injuries or pain, ones non-reparable by an intervention, receive little attention.

The most common sclerotherapy complications include various levels of skin damage in approximately 10% of the cases. Other relatively common complications are nerve injuries, muscle fibrosis, post-procedural infections, and transient haemoglobinuria. Less frequent but severe complications include renal damage, severe bleedings, pulmonary embolism, pulmonary hypertension and oedema, and cardiac collapse. Ethanol-usage reportedly produces the highest complication rates (201,203,204). Overall complication rates show a dramatic range of 0 to 61%, depending on the study and its definition of a treatment complication (200,203,206,212,217-222).

5.3.8.4. Laser therapy

Endovascular laser therapy, mainly by diode or YAG laser, has during recent years gained ground in treating VMs. Such therapy is suitable for selected lesions, and it can be performed as a staged procedure, as sclerotherapy. Current research data on endovascular laser therapy for VMs is relatively scarce; however, the existing outcome and complication results are promising (197,223-226). A recent study from Simon and colleagues found endovascular laser therapy to provide good symptom relief for 32 patients with aerodigestive tract VMs suffering from sleep apnea: they showed significant reduction in dysphagia, in sleepiness score, and in apnea-hypopnea index, and the treatment diminished patients' need for positive-air-pressure equipment (227).

5.3.8.5. Pharmacological management

Rapamycin, an mTor inhibitor, is a recently introduced treatment option for VMs resistant to other therapies. It blocks the VM-causative PI3K/AKT-signalling pathway, and limits lesion progression. Future clinical use and research will reveal the role for this drug in treatment strategy for VMs (169).

5.3.9. Prognosis

Venous malformation is a chronic condition. The aim of any treatment is to limit the symptoms and morbidity, and to improve the quality of life. Sclerotherapy has been efficient in improvement of the quality of life for VM patients after a follow-up period of one year (222,228); yet, long-term outcomes and quality of life measurements as well as prospective randomized studies are lacking, mostly due to the rarity of this condition plus many heterogenous treatment protocols and study settings (202,203). Despite most therapies, VMs tend to gradually recur, emphasizing the necessity of an interdisciplinary approach in follow-up and treatment planning, the main goal being efficient symptom relief with acceptable side-effects, no matter the treatment modality (4).

6. Aims of the study

This study concentrates on infantile haemangioma and venous malformation. It aims to elucidate the risk factors for and inheritance model of IH, and to critically evaluate the safety of sclerotherapy treatment for VMs. The objective is to answer the following questions:

1. What are the risk factors for complicated, morbidity-inducing infantile haemangiomas? Do perinatal risk factors for IH differ in our study population from those reported in earlier studies in other populations?

2. What are the characteristics of familial infantile haemangiomas? What inheritance patterns can be identified for familial infantile haemangiomas?

3. What are the sclerotherapy complications for head and neck venous malformations? How common are the complications? How severe are the complications according to a standardized classification? What VM-related and technical characteristics affect the complication risk?

4. What are the sclerotherapy complications for trunk and extremities venous malformations? How common are the complications? How severe are the complications according to a standardized classification? What VM-related and technical characteristics affect the complication risk?

7. Patients and Methods

7.1. Ethical considerations

All study protocols were approved by the Helsinki University Hospital's ethics committee. The study protocols followed good clinical practice and conformed to the Declaration of Helsinki. All patients and their caregivers taking part in infantile haemangioma studies signed an informed consent. Our VM patient data consisted of retrospective chart reviews.

7.2. Helsinki University Hospital district

Helsinki University Hospital (HUH) is a referral centre serving 1.5 million inhabitants in southern Finland. It maintains a comprehensive electronic hospital record covering all disciplines, excluding primary health care records. All patients in these studies have been treated and followed in HUH. Since 2002, an interdisciplinary vascular anomaly team of HUH has coordinated the diagnostics, treatment, and follow-up of patients with extracranial vascular anomalies. It also receives referrals concerning vascular anomalies from other hospital districts in Finland. The interdisciplinary team consists of paediatric, plastic, and maxillofacial surgeons, otorhinolaryngologists, dermatologists, ophtalmologists, pathologists, and radiologists.

7.3. Risk factors for and inheritance of infantile haemangioma

We identified from electronic hospital records all patients who had visited HUH's paediatric vascular anomaly clinic between 2004 and 2007 with diagnosis D18.0 (haemangioma), or Q82.5 (birthmark), based on the 10th International Classification of Diagnoses (ICD-10). For the 263 patients who matched these criteria, we examined their electronic hospital records. Based on patients' clinical characteristics, typical clinical course during follow-up, photography, and imaging studies, we found 185 patients with infantile haemangioma. The remaining 78 patients either had a congenital haemangioma (7), undefined haemangioma (17), or other vascular anomaly or birthmark (54), and they were excluded from the study. For the 185 children with IH, we noted gender, ethnic background, current age, and age at the first and last visit to HUH. We recorded all IH-related complications and interventions.

We registered the number of IH lesions, location, and subtype, and classified each IH's morphological subtype as focal, multifocal (≥10), segmental, or indeterminate based on the lesion with most clinical relevance. To investigate IH patients' gestational and perinatal factors from hospital records, we collected all information available on gestational age, multiple gestations, birth weight, first-minute Apgar score, type of delivery, any possible other diseases, positive family history of IH, plus maternal age, in vitro fertilization therapy (IVF), gestational diabetes mellitus (GDM), preeclampsia (PE), placenta praevia, chorionic villus sampling (CVS), other maternal diseases, mothers' medications, and cigarette smoking during pregnancy. Only part of these data appeared in IH children's records, and we were not allowed to access mothers' hospital records.

Patient questionnaire and interview

We contacted patients with a confirmed IH diagnosis and their caregivers with a questionnaire to acquire information on perinatal, maternal, and gestational information, the child's current diseases, family history of an IH, and other treatments for IH occurring outside of HUH (Article II, Appendix 1). We requested data on these patients' current subjective IH-induced long-term discomfort on the visual analogue scale (VAS) ranging from 1 (no discomfort) to 10 (very significant discomfort). To achieve a maximal response rate, the questionnaire was sent three times if necessary.

We re-contacted by phone those families who reported a positive IH family history and permitted re-contacting to record the family pedigrees. The course of IH in affected family members, its location, and the number of lesions for all the affected family members were confirmed. We also asked families about any other inherited diseases in the family. The birthplaces of the grandparents of the IH-affected family side were recorded in order to identify regional clustering and possible founder effect. If the grandparents' birthplace was unknown, the parents' birthplaces were registered.

Analysis of the inheritance patterns and geographic distribution of IH families was based on these data.

Reference data

The diagnostic challenges regarding vascular birthmarks and the misuse of the term "haemangioma" disallowed our sending the questionnaire to a randomly selected control group, as this would have yielded most likely many false-positive but also false-negative IH cases (5,15,42,112). Therefore, to analyse the perinatal, gestational, and maternal risk factors for IH, we acquired our hospital district's pre- and perinatal statistics on live childbirths within the same catchment area, 2004-2007, from the Finnish National Institute for Health and Welfare (THL). These data served as our reference material, as they represent well the average newborns in our hospital district; however, due to differing sources of data for the IH patients and reference individuals, we regarded this also as a limitation. The THL annually receives information on all childbirths as well as their perinatal events, maternal health, and demographic characteristics from maternity and obstetrics clinics, clinics that all follow the national guidelines for the diagnostics of gestational diseases. The THL maintains the Finnish Medical Birth Register (FMBR). After data linkages to our Central Population Register for live births and Cause-of-Death Register for stillbirths and infant deaths, the FMBR covers all newborns in Finland.

Statistics

Only patients with a confirmed IH diagnosis underwent statistical analysis. For analysis regarding gender, number of IH lesions, location, complications, and interventions, we included all patients for whom the information was available.

Patients with one or more IH-affected relatives were considered to be familial cases. We undertook the statistical analysis by comparing all familial IH cases to sporadic cases, and those familial IH cases with an affected first-degree relative to sporadic cases regarding IH, perinatal, and long-term morbidity data, based on all available data acquired from the patient records and questionnaire.

To analyse and to compare the perinatal, gestational, and maternal factors in our IH cohort to FMBR data of the same catchment area and time period, we included only patients who had responded to the questionnaire in order to avoid any positive reporting bias on perinatal complications in child's hospital records. This bias was due to the fact that we only had access to the child's records but not the mother's: it was therefore more likely that in cases with any gestational or perinatal complication, this was usually reported in the child's records, whereas an uncomplicated perinatal period was often left unreported. We also show the rates based on all available information.

For continuous variables, comparison between two independent groups was by the Mann-Whitney U-test. For categorical variables, we used the Chi-Square test, or,

when Chi-Square test preconditions were not met, Fisher's exact test. For bivariate analysis, Mantel-Haenszel and heterogeneity tests were applied. All analyses were performed with NCSS8 Statistical Software.

7.4. Sclerotherpy for venous malformations

We identified patients treated with sclerotherapy for either head and neck, or trunk and extremity VMs between 1 January 2007 and 31 August 2013 from the Hospital's electronic radiology information system. We based VM diagnosis on clinical evaluation, MRI, and ultrasonography imaging according to the criteria of the ISSVA classification (18). We recorded VM patients' demographic details, the VM location and tissue involvement, possible previous surgery, number of sclerotherapy sessions, sclerosants, administration of perioperative corticosteroid for head and neck VMs, alterations in coagulation factors for trunk and extremity VMs, other treatment modalities used, follow-up, and sclerotherapy complications. For facial VMs, we recorded location further into subgroups of lower face, mid-face, upper face, neck, oral cavity, orbit, or a combination of these. The tissues affected by the VM were classified as subcutaneous, submucosal, intramuscular, intraosseal, intra- or retroperitoneal, intra-articular, or a combination of these.

Sclerotherapy procedure

Indications for sclerotherapy included pain, functional impairment, or aesthetic impairment, compromise of vital structures, or coagulation disturbance. The interdisciplinary team assessed the treatment indication individually for each VM patient. A trained interventional radiologist performed all sclerotherapies.

During the sclerotherapy procedure, access to the VM lesion was obtained by cannulating the VM with one or several needles under ultrasound guidance. Retrograde blood flow confirmed the intravenous access. Then, fluoroscopy by iodinated contrast injection served to assess VM architecture and draining veins. If the venous drainage circulated through critical venous routes or was rapid, the draining veins were either mechanically blocked or compressed. For most sclerotherapies, we used this same draining technique to prevent overfill of the VM, and systemic leakage of the sclerosant, but also to ensure the draining of the whole lesion to achieve sufficient response. In case of small, superficial VMs with good patient co-operation, local anaesthesia and conscious sedation was sufficient. For larger and deeper VMs in delicate or painful areas, or for ones potentially threatening the airways or other vital structures, sclerotherapy was executed under general anaesthesia.

For all head and neck, and for most trunk and extremity VMs, we used only percutaneous sclerotherapy. In 4.2% of procedures for trunk and extremity VMs, we used adjuvant endovascular techniques to obtain a sufficient response. The indication for adjuvant therapies involved mostly large, demanding VMs, in which sole sclerotherapy was assessed as insufficient. These regimes included n-butyl-2-cyanoacrylate glue for closing very large venous spaces, coils for closing the VM's draining veins, particles for embolizing VM-feeding arteries, or an intravascular laser for very large VMs.

Sclerosants

We used mainly foaming detergent sclerosants (3% sodium tetradecyl sulfate (STS) or polidocanol 5-30 mg/ml) and rarely bleomycin (1 mg/ml), 95% ethanol, doxicyclin, or a combination of sclerosants, the first-line choice being mainly STS. For small VM lesions, polidocanol was often chosen, as different concentrations are available. For VMs in confined locations at risk for undesired oedema and potential nerve compression, we preferred bleomycin. Ethanol was rarely used, and it mainly served in combination with other sclerosants for extensive lesions, responding poorly to other sclerosants.

Periprocedural treatment

For patients with large VMs, we monitored the blood D-dimer and fibrinogen prior to the procedure and consulted a haematologist when necessary. In cases of an extensive trunk and extremity lesion, we monitored urine haemoglobin and volume. Patients with large VMs or at high complication risk remained in hospital until stable. Those patients at low complication risk stayed only for 2 to 3 hours in the hospital after the treatment. For VMs at risk for extensive oedema, or for VMs in confined locations, perioperative corticosteroid was administered. To further inhibit post-procedural tissue swelling and to favour closure of the vascular channels, we recommended the patient to wear a compressive garment if such was applicable. All patients were advised to contact the hospital in case of any complications.

Consecutive therapies and follow-up

Small VM lesions resolved mostly with only one sclerotherapy session. For extensive VMs, we scheduled several sclerotherapies in series, as they were anticipated to require multiple sessions. Most patients were clinically monitored for approximately 3 to 6 months after sclerotherapy. If the treatment response was sufficient at the follow-up, the patients were advised to contact our clinic in case of recurrence or symptoms. If the symptoms persisted despite repeated sclerotherapies, the interdisciplinary team evaluated the possibilities of other treatment modalities. For example, even after their venous channels had been closed with sclerotherapy, some large lesions required de-bulking surgery. Passive follow-up time was recorded from the last sclerotherapy to the study date. Because of the lack of any other hospitals providing treatment for vascular anomalies in our hospital district, it was very unlikely that a VM patient would have sought treatment from any other institution.

Complication assessment

With all available data from hospital records concerning the sclerotherapy complications and management of the complications, we assessed all sclerotherapy complications retrospectively in our interdisciplinary team. Based on the team's consensus, the grade for each complication was set according to the Clavien-Dindo classification (Table 6) (214-216) .

Table 6. Clavien-Dindo classification of complications (215). Reprinted with the permission of Wolter Kluwer Health from Dindo D. et al. "Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey." Ann Surg. 2004 Aug; 240(2):205-13.

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention not under general anaesthesia
IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (CNS complications)* requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multi-organ dysfunction
V	Death of a patient
Suffix 'd'	If the patient suffers from a complication at the time of discharge, the suffix "d" (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

* Brain haemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks. Abbreviations: CNS: central nervous system; IC: intensive care; ICU: intensive care unit.

Statistics

Analyses for variables predicting complications were executed with Chi-Square test, or when the preconditions were not met, with Fisher's exact test. Mann-Whitney's test served for analysis of continuous variables. A P-value of <0.05 was considered statistically significant. Microsoft Office Excel 2007 and NCSS8 Statistical Software served for data analysis.

8. Results

8.1. Risk factors for and inheritance of infantile haemangioma

We identified initially 263 patients, of whom 185 had a true infantile haemangioma and were included in the study. Of these patients, 134 (72%) were female, and 51 (28%) were male. Most patients originated from Finland; 9% had both parents and 8% one parent originating outside of Finland. These patients visited our clinic for the first time on average at the age of 12 months (median 7 months, range 1-158 months), and were followed until the age of 5 years (median 60 months, range 4-158 months).

Patient questionnaire

Of the 185 patients and their families, 136 (74%) responded to the questionnaire. We found no difference in ethnic background, nor in perinatal, maternal, nor gestational profile between those whose caregivers responded and those failing to respond. The IH patients were on average 10 years old (range 7-20 years) at the time the questionnaires went out.

IH number, location, and subtype

In total we counted 332 IH lesions (median 1; range 1-30 IHs). Of these 185 children, 50 (27%) had multiple (>1) IHs, and these children were significantly more often female (p=0.032, OR 2.45, 95% CI 1.06-5.67). Head and neck localisation occurred most commonly: IH located in the face in 42% of the children, in other parts of the head in 14%, in the neck in 11%, and in the trunk in 44%. The IH lesion located in the upper limb in 12% and in the lower limb in 14%. The IH subtype was focal in 75%, segmental in 4%, multifocal in 1%, and indeterminate in 20%.

Risk factors for IH localization and subtype

We observed that chorionic villus sampling had taken place significantly more frequently during the gestation of those children with an IH in the upper limb compared to other locations (p=0.036, OR 4.8, 95% CI 1.18-19.50). History of gestational diabetes mellitus did somewhat predict a facial IH location: of the 13 children undergoing GDM, 9 (69%) manifested a facial IH; this difference was, however, statistically non-significant (p=0.082, OR 3.05, 95% CI 0.90-10.35). We observed no other associations between perinatal, gestational, nor maternal factors with IH location or subtype.

IH complications and intervention

Complications of IH affected, among the 185 patients, 65 (35%). The most common complications were ulceration and visual axis compromise. Intervention was necessary for 68 (37%). The most common interventions were pulsed-dye laser and

surgery, because these children were born prior to the introduction of β-blocker therapy (Table 7).

Table 7. Summary of IH complications and interventions for the 185 IH children in our cohort. Patients may have had more than one complication. Re-printed and modified from the original article with the permission of John Wiley & Sons Ltd.

IH complications	**N (%)**
Ulceration	48 (26)
Visual axis compromise	18 (10)
Airway obstruction	4 (2)
Cardiac compromise	2 (1)
Auricular canal obstruction	1 (0.5)
Interventions for IH	
Pulsed-dye laser	36 (19)
Surgical scar correction	25 (14)
Surgical removal	20 (11)
Eye patching	13 (7)
Systemic corticosteroid	12 (6)
Local corticosteroid injections	5 (3)
Other interventions (embolization, radiofrequency ablation)	8 (4)

Risk factors for IH complications, interventions, and long-term discomfort

Ulceration occurred significantly more often in preterm IH children than in term infants (p=0.041, OR 2.29, 95% CI 1.02-5.14). Complications, interventions, and long-term discomfort rates were unaffected by any other perinatal, gestational, or maternal factor. We observed elevated complication, intervention, and discomfort rates in IH children with facial and neck locations, and in IHs of segmental and indeterminate subtypes. Focal and truncal IHs were at lower risk for adverse events (Tables 8 and 9). The reported average long-term discomfort rate in the whole cohort was 2.31 on the VAS scale from 1 to 10, and was mostly due to aesthetic or psychosocial concerns.

Table 8. Summary of characteristics of infantile haemangioma (IH) that significantly either elevate (↑) or reduce (↓) the risk for any IH complication, IH ulceration, or intervention. Re-printed and modified from the original article with the permission of John Wiley & Sons Ltd.

IH / patient characteristics	Elevated (↑) or reduced (↓) risk for		% (N)	P value	OR (95% CI)
Perinatal					
Preterm birth	Ulceration	↑	41 (13/32)	0.041	2.29 (1.02-5.14)
IH subtype					
Segmental	Complication	↑	100 (7/7)	<0.001	45.9 (2.55-824)
	Ulceration	↑	57 (4/7)	0.037	5.53 (1.17-26.2)
	Intervention	↑	100 (7/7)	<0.001	39.5 (2.21-709)
Indeterminate	Complication	↑	65 (24/37)	<0.001	5.70 (2.62-12.4)
	Ulceration	↑	46 (17/37)	<0.001	3.53 (1.63-7.62)
Focal	Complication	↓	25 (34/139)	<0.001	0.16 (0.08-0.32)
	Ulceration	↓	19 (27/139)	<0.001	0.20 (0.10-0.41)
	Intervention	↓	27 (38/139)	<0.001	0.18 (0.09-0.37)
IH location					
Facial	Complication	↑	47 (36/77)	0.005	2.39 (1.30-4.44)
	Intervention	↑	53 (41/77)	<0.001	3.25 (1.75-6.05)
Neck	Ulceration	↑	45 (9/20)	0.040	2.64 (1.02-6.84)
Trunk	Complication	↓	27 (22/82)	0.035	0.51 (0.27-0.96)
Other factors					
Complication	Intervention	↑	78 (51/65)	<0.001	20.6 (9.51-44.8)

Abbreviations: CI: Confidence Interval; OR: Odds Ratio; Preterm: <37gestational weeks

Table 9. Summary of IH characteristics that significantly either elevate or reduce long-term discomfort rate, evaluated on visual analogue scale (VAS) from 1 to 10. Re-printed and modified from the original article with the permission of John Wiley & Sons Ltd.

Variable	Long-term morbidity VAS 1-10 (95% CI)	P value
Long-term morbidity elevated		
Any complication	3.0 (2.4-3.7)	<0.001
Any intervention	2.9 (2.2-3.6)	<0.001
Segmental subtype	4.8 (1.2-8.3)	0.004
Facial location	2.6 (2.0-3.1)	0.039
Indeterminate subtype	2.7 (1.8-3.7)	0.045
Long-term morbidity reduced		
Truncal location	1.6 (1.4-1.9)	0.009
Focal subtype	1.9 (1.6-2.2)	0.010

Abbreviations: CI: Confidence Interval; VAS: Visual analogue scale

Perinatal, gestational, and maternal risk factors

Table 10 summarizes IH children's perinatal, gestational, and maternal figures compared to the FMBR rates in 2004-2007 covering the same catchment area. In addition to other risks, maternal gestational diabetes was more common in the IH children's mothers than listed in the FMBR (p=0.005, OR 2.62, 95% CI 1.39-4.95). Based entirely on hospital records and before sending the questionnaire, we were aware of 46% (6 of 13) of all GDM pregnancies, of 70% (16 of 23) of preeclampsia cases, of 44% (4 of 9) of IVF cases, of 20% (1 of 5) of placenta praevia cases, and of 11% (2 of 18) of CVS.

Table 10. Perinatal, maternal, and gestational characteristics of the IH children in responses to the questionnaire: column I, (IH Q, n=136). All available data based on hospital records and questionnaire: column II, (IH all, n=185). Finnish Medical Birth Register data: column III (FMBR, n=70 842). P values, odds ratios (OR), and 95% confidence intervals (CI) are calculated between columns I and III by Chi-Square Test for univariate analysis, and by Mantel-Haenszel and heterogeneity tests for bivariate analysis. Re-printed and modified from the original article with the permission of John Wiley & Sons Ltd.

Variable	I IH Q %	II IH all %	III FMBR %	P value	OR (95% CI)
Perinatal factors					
Female	73.5	72.4	49.0	<0.001	2.89 (1.98-4.22)
Twins	12.4	10.9	3.0	<0.001	4.05 (2.38-6.89)
Preterm infants	16.2	18.7	6.2	<0.001	2.93 (1.86-4.61)
Very preterm infants	5.9	7.6	0.9	<0.001	6.70 (3.31-13.5)
Birth weight <2500g	14.0	17.6	4.1	<0.001	3.76 (2.32-6.06)
Apgar score ≤6	11.3	11.5	4.7	0.002	2.56 (1.47-4.55)
Maternal and gestational factors					
Mothers aged ≥35 y	32.1	30.3	22.3	0.009	1.64 (1.15-2.36)
First childbirth	55.9	55.9	45.6	0.020	1.51 (1.08-2.12)
IVF	6.6	5.9	3.3	NS	2.09 (1.07-4.06)
IVF in mothers ≥35 y	16.3	14.9	6.6	NS	3.00 (2.76-3.23)
CVS	8.3	8.3	2.4	<0.001	3.73 (2.03-6.86)
CVS in mothers ≥35 y	21.4	18.9	6.8	NS	6.55 (6.00-7.16)
Placenta praevia	4.3	3.4	0.3	<0.001	13.4 (5.58-32.3)
GDM	7.4	8.2	3.0	0.005	2.62 (1.39-4.95)
GDM in mothers ≥35 y	9.3	11.8	4.9	NS	2.10 (1.85-2.37)
PE	10.4	14.3	2.4	<0.001	4.70 (2.71-8.15)
PE in mothers ≥35 y	14.0	17.6	2.5	NS	1.05 (0.88-1.24)
PE in first childbirth	14.5	20.7	3.3	NS	2.08 (1.81-2.38)
Maternal smoking	9.7	10.1	13.6	NS	0.61 (0.34-1.10)
Maternal β-blocker use	3.7	4.3	0.7	<0.001	5.56 (2.33-13.3)

Abbreviations: CVS: chorionic villus sampling; FMBR: Finnish Medical Birth Register; GDM: gestational diabetes mellitus; IH: infantile haemangioma; IVF: *in vitro* fertilization; NS: nonsignificant statistical difference; OR: odds ratio; PE: preeclampsia; Preterm: < 37 gestational weeks; Very preterm: < 32 gestational weeks or < 1500 g; y: years.

Inheritance of IH

Of the whole cohort, information on IH family history was available in 141 cases; in 50 (35%) families it was positive, of which in 34 (68%) cases the closest affected was a first-degree relative. Among those 136 IH families who responded to the questionnaire, 46 (34%) of the families reported a positive family history of IH.

Comparison of IH characteristics and risk factors in familial and sporadic IHs

IH characteristics and risk factors between all familial cases and sporadic IH cases were closely similar. Only the number of identical twins between the groups differed, as all three monozygotic twins of this cohort also had first-degree relatives with IH, whereas no monozygotic twins appeared in the sporadic IH group (p=0.046, OR 21.0, 95% CI 1.05-418.2). Because of the low number of monozygotic twins in the cohort, the confidence interval became large. IH patients with IH-positive first-degree relatives reported a significantly higher long-term discomfort rate (2.52, 95% CI 1.87-3.16) than did the sporadic cases (2.03, 95% CI 1.64-2.42), p=0.036.

Families with many IH-affected members

Of the 46 families reporting positive family history of IH, we only reached 40, as 3 did not allow re-contact, and 3 were unreachable. The number and characteristics of IH-affected family members are in Table 11. IH number, location, and subtype did not seem to correlate between IH-affected members within the same family. Of note, one index IH patient with a periorbital IH had an identical twin sister with an IH in exactly the same location (see Figure 2 in article 2. in the Appendix). No clear clustering of other inherited diseases or syndromes was observable in these families.

Table 11. Summary of IH-affected families.

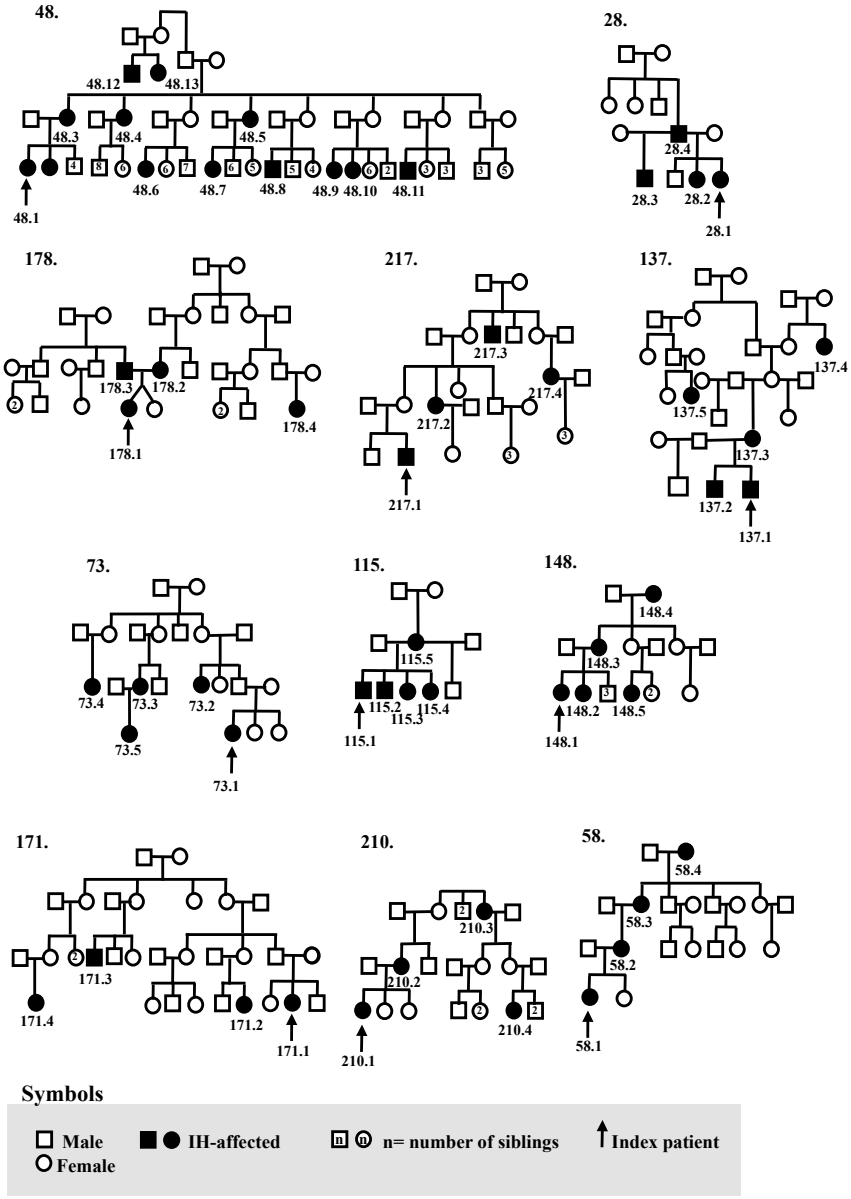
Characteristics of 40 families with several IH-affected members	**N (%, or median and range)**
Average number of IH-affected members per pedigree	3 (2, 2-13)
Number of all IH-affected family members, excluding the index IH patient	81
Number of IH-affected women	59 (73)
Number of IH-affected men	22 (27)
Mother of the index patient with an IH	13 (33)
Father of the index patient with an IH	4 (10)
Pedigrees including first-degree relatives	25 (63)
Pedigrees including second-degree relatives	10 (25)
Pedigrees including more distant relatives	5 (12)
Pedigrees with maternal side of family affected	22 (55)
Pedigrees with paternal side of family affected	12 (30)
Pedigrees with only siblings affected	6 (15)

Of the 40 families, 11 had 4 or more IH-affected family members. Pedigrees with four or more affected first- or second-degree relatives (Figure 21) indicated that the transmission seemed to follow an autosomal dominant inheritance pattern with incomplete penetrance: in one pedigree (no. 28), the father had transmitted the IH to three of his four children, suggesting strong dominant transmission. In ten pedigrees, however, the inheritance pattern could also indicate maternal transmission with incomplete penetrance.

Geographic clustering

The places of birth of the affected families' grandparents ranged widely throughout Finland, as would be expected, clustering in southern Finland, corresponding to our hospital-district area. Nevertheless, many grandparents originated from low-population eastern Finland. We observed, however, no clear founder effect nor geographic clustering.

Figure 21. Pedigrees of cohorts having four or more family members with an IH. Reprinted and modified from the original article with the permission of American Academy of Pediatrics.



IH-related diseases, syndromes, and inherited diseases of the cohort

Atopic disease occurred in the whole cohort in 22% of these children; it was equally frequent in children with and without a positive IH family history. One IH child in our cohort had PHACES syndrome, and another child presented with Sotos syndrome (cerebral gigantism), each with a negative IH family history. One girl had Turner's syndrome, as well, and her mother also had had an IH. Other genetic disorders within our IH cohort, with no IH family history, were APC resistance and type 1 neurofibromatosis, each affecting only one child.

8.2. Sclerotherapy for venous malformations

Complications occurred in 13 (17.3%) head-and-neck VM patients and were subjected to 15 sclerotherapy sessions (10.0%). For trunk-and-extremity VM, complications affected 31 (24.4%) patients, and occurred in relation to 35 (12.5%) sclerotherapy sessions. Demographic characteristics were similar between the complicated and non-complicated patients. For head and neck VMs, those who suffered from any complication also underwent more sclerotherapies (p=0.009), needed more surgery after sclerotherapy (p=0.007), and had longer clinical follow-up after sclerotherapy (p=0.01). Table 12 summarises the VM patient characteristics, sclerotherapies, other treatments, and follow-up.

Table 12. Summary of venous malformation (VM) patient characteristics and sclerotherapies during the follow-up period for head and neck (H&N) and trunk and extremity (T&E) VMs. Re-printed and modified from the original articles with the permission of Springer and SAGE Publications.

Variable	H&N N (%) or median (range)	T&E N (%) or median (range)
Patients	75	127
Females	51 (68.0)	73 (57.5)
Males	24 (32.0)	54 (42.5)
Total number of sclerotherpies in the cohort	150	280
Sclerotherapies per patient	1.0 (1-13)	2.0 (1-10)
Age (years)	33.0 (3-75)	21.5 (3-76)
Surgery prior to sclerotherapy	27 (36.0)	29 (22.8)
Surgery after sclerotherapy	6 (8.0)	10 (7.9)
Clinical follow-up (months) from first session	6.0 (0-80)	35.0 (0-82)

Sclerotherapy outcome was assessed only for head and neck VMs. Due to the retrospective study setting, outcome evaluation was limited to hospital records. Of those VM patients without complications, only 10 (16%) had a non-satisfactory outcome with further sclerotherapy planned, only 4 (6%) needed other treatment modalities due to non-satisfactory sclerotherapy outcome, and only 1 (2%) had a non-satisfactory outcome without further treatment modalities scheduled at the time of the research. Of those VM patients with complications, 2 (15%) receive further sclerotherapies despite unsatisfactory sclerotherapy outcome thus far, 4 (31%) needed other treatments after sclerotherapy, and 1 (8%) has an unsatisfactory outcome with no other recommendable treatment modalities. The cohort's average follow-up from hospital records from the last sclerotherapy to the time of this study was 36 months (median 35 months, range 4-81 months).

VM locations and tissue planes

For head and neck VMs, the location and tissue involvement between those who suffered from a complication and those with no complication did not differ (Table 13). Lesions involving the orbit and traversing many tissue planes were rare but did show relatively high complication rates. No statistically significant difference appeared. Those complications related to orbital VM lesions included prolonged swelling and pain and transient colour blindness with eye-muscle palsy. However, in trunk and extremity VMs, the complication risk for subcutaneously located lesions was significantly higher than for those with deeper lesions with an intramuscular component (p=0.049).

Table 13. Summary of localisation and tissue involvement of the venous malformations in head and neck (H&N) and trunk and extremity (T&E) cohorts. Re-printed and modified from the original articles with the permission of Springer and SAGE Publications.

Variable	**H&N** **N (%)**	**T&E** **N (%)**
Location		
Lower face	5 (6.7)	
Mid-face	18 (24.0)	
Upper face	2 (2.7)	
Orbital extension	3 (4.0)	
VM with orbital connection	3 (4.0)	
Oral cavity	23 (30.7)	
VM with oral cavity connection	16 (21.3)	
Neck	5 (6.7)	
Trunk		15 (11.8)
Upper extremity		50 (39.4)
Lower extremity		62 (48.8)
Tissue plane		
Subcutaneous / -mucous	33 (44.0)	59 (46.5)
Intramuscular	13 (17.3)	64 (50.4)
Intraosseal	2 (2.7)	5 (3.9)
Intra-articular		4 (3.2)
Intra-abdominal, retroperitoneal		2 (1.6)
> 1 tissue plane involved	27 (36.0)	

Sclerosing agents

STS and polidocanol were the sclerosants most commonly applied. Use of ethanol, bleomycin, or doxycyclin was rare. Ethanol was mainly combined with other sclerosants. In sclerotherapies for head and neck VMs, we observed no significant difference regarding the sclerosant's complication risk. For trunk and extremity VMs, sclerotherapies that involved the ethanol produced significantly more complications than did detergent sclerosants (STS and polidocanol) (p=0.019) (Table 14).

Table 14. Summary of sclerosing agents and respective complication rates used in sclerotherapies for head and neck (H&N) and trunk and extremities (T&E) venous malformations.

Sclerosant	**H&N**		**T&E**	
	Number of procedures (total n=150)	**Number of procedures with complications (%)**	**Number of procedures (total n=280)**	**Number of procedures with complications (%)**
STS	96	7 (7.3)	189	21 (11.1)
Polidocanol	17	1 (5.9)	51	6 (11.8)
STS and polidocanol combined	12	0		
Ethanol only	1	0	3	2 (66.7)
Ethanol in combination	7	2 (28.6)	16	5 (31.3)
Bleomycin only	3	1 (33.3)	4	0 (0.0)
Bleomycin in combination	10	3 (30.0)	12	1 (8.3)
Doxycycline	2	1 (50.0)	1	1 (100.0)
Detergent sclerosant, not specified	2	0	4	0

Abbreviations: n=number of patients; STS: Sodium tetradecyl sulphate.

Complications in sclerotherapy

Complications affected altogether 44 VM patients and occurred in 51 sclerotherapy sessions during the follow-up period (Table 15). For head and neck VMs, 80%, and for trunk and extremity VMs, 83% of complications were graded I to II and resolved without treatment or with conservative methods. We discuss below the grade III and IV complications.

Table 15. Summary of sclerotherapy complications, graded according to the Clavien-Dindo classification from I to V. Re-printed and modified from the original articles with the permission of Springer and SAGE Publications.

Location	Complication	Management	N	Grade (I-V)
H&N	Unusual and prolonged hematoma and swelling	Not necessitated	3	I
H&N	Partial facial nerve palsy	Not necessitated	1	I
H&N	Mucous necrosis in the oral cavity	Not necessitated	2	I
H&N	Partial palsy in the superior rectus eye muscle with transient colour blindness	Not necessitated	1	I
H&N	Prolonged pain	Analgesics	1	Id
H&N	Numbness of the lip / tongue	Not necessitated	2	I
T&E	Skin damage	Not necessitated	8	I
T&E	Pain or swelling or both for > 2 weeks	Analgesic and/or compression garment	6	I
T&E	Thrombophlebitis external to VM	Not necessitated	3	I
T&E	Unusual pain and transient sensory loss	Analgesic	1	I
T&E	Unusual swelling and loss of range of joint motion	Physiotherapy	1	I
T&E	Pain, swelling, skin damage and loss of range of motion	Analgesic, physiotherapy	1	I
T&E	Loss of digital joint motion	Physiotherapy	1	I
H&N	Infection and abscess of the injection site	Bedside revision and oral antibiotics	1	II
H&N	Mucous ulceration and infection	Oral antibiotics	1	II
T&E	Skin damage, infected	Oral antibiotics	4	II
T&E	Allergic reaction	Corticosteroids, antihistamine	3	II
T&E	Intra-abdominal bleeding, mild	Blood transfusion (one unit)	1	II
T&E	Deep vein thrombosis at ankle level	LMWH medication	1	II
T&E	Skin damage	Skin graft under local anaesthesia	2	IIIa
H&N	Partial necrosis of the maxillary bone and 3 teeth, infraorbital nerve injury	Surgical removal of the necrotic tissue	1	IIIb
H&N	Deep skin and frontal muscle necrosis, partial facial nerve palsy	Several surgical revisions and skin grafting.	1	IIIb
H&N	Severe bleeding of the tongue, partial tongue necrosis, sepsis	Embolization, surgical removal of the necrotic tissue, iv antibiotics	1	IVa
T&E	Injection site bleeding, sepsis, abscess, worsening of DIC	Blood and coagulation factor transfusion, abscess drainage, iv antibiotics, ICU treatment, prolonged hospitalization	1	IVb
T&E	Injection site bleeding, sepsis and skin damage	ICU treatment and prolonged hospitalization, iv antibiotics	1	IVb
T&E	Massive intra-abdominal bleeding	Intra-arterial embolization, blood transfusion, ICU treatment	1	IVb
T&E	Lethal intracerebral haemorrhage		1	V

Abbreviations: H&N: head and neck; ICU: intensive care unit; LMWH: low-molecular-weight heparin; T&E: trunk and extremity.

Severe complications of sclerotherapy

A 29-year-old woman had a submucosal VM in her palate causing some discomfort before any interventions. She underwent one sclerotherapy with STS. Despite the seemingly normal course of sclerotherapy, occlusion of the internal maxillary artery and its peripheral vascular bed occurred. This resulted in necrosis in the maxilla, and three teeth, requiring surgical removal of the necrotic tissues, graded as a IIIb complication. As a result, she has a permanent bone defect, allodynia, and infraorbital nerve injury (Article III).

A 31-year-old woman suffered from episodes of headaches due to a large subcutaneous and intramuscular VM in the temporal region, one that was connected to intracranial veins. She had undergone surgery almost 20 years prior to sclerotherapy. Her first sclerotherapy was successful but not sufficient for symptom relief. After the second scleotherapy with STS, without any deviation from the normal procedure, she developed first a facial nerve palsy and then skin and muscle necrosis in the frontotemporal area. These complications necessitated several revisions and correction with a skin graft, and later scar corrections. Other functions of the facial nerve recovered, but her right frontal muscle function was lost. Partial hair loss occurred in the grafted temporal scalp area. The mechanism of the complication remains unclear but may have been related to the tissue toxicity of STS. We considered this to be a grade IIIb complication (Article III).

A large intramuscular VM in the tongue caused functional impairment of eating and speaking for a 69-year-old man with diabetes type 2 who was on acetylsalicylic acid medication. To avoid extensive swelling near the airways, the sclerotherapy was primarily performed with bleomycin. During the session, an unexpected bleed occurred from a large area of tongue's capillary bed. His tongue was compressed with a thrombin product, and ethanol and STS were also injected to create swelling and compression. Despite these measures, the bleed continued and necessitated catheterization of the right lingual artery and injection of embolizing particles into the capillaries. This led to partial tongue muscle necrosis and infection. He developed sepsis, required intravenous antibiotics and surgical removal of the necrotic tissue, resulting in permanent partial loss of the tongue. The patient suffers from some problems with articulation, but is satisfied with the overall result. We considered this to be a life-threatening complication and single organ dysfunction, thus, earning a grade IVa complication (Article III)

A large and diffuse retroperitoneal VM in a paediatric patient necessitated intervention; untreated it caused the patient severe consumption coagulopathy. The lesion was considered inoperable. Following a dorsal needle puncture of the VM, he developed a severe intra-abdominal bleed from the left phrenic artery. The bleed necessitated intravascular embolization and hospitalization in the intensive care unit.

Despite this complication, he underwent thereafter several sclerotherapies to achieve stabilization of the VM-induced coagulopathy (Article IV).

A young man suffered from a very extensive VM in the lower body and right leg, causing severe consumption coagulopathy and resulting in pulmonary embolism and life-threatening bleedings due to very low fibrinogen levels prior to sclerotherapy. The VM was considered inoperable because of the high risk of bleeding. The case was thoroughly discussed in our interdisciplinary team together with a haematologist, because the complication risk during scleortherapy was regarded very high. An intervention was necessary to control the coagulopathy and to facilitate further surgery. During two separate sclerotherapies, he suffered from serious infections. Following the first sclerotherapy with polidocanol and ethanol combined with NBCA glue and laser treatment, severe bleeding occurred at the injection site, leading to a large haematoma, infection, and sepsis necessitating intravenous antibiotics and prolonged hospitalisation. After the second sclerotherapy combined with laser and NBCA glue, the intravascular coagulopathy worsened, leading to bleeding, abscess formation, and septic infection, necessitating blood and coagulation transfusion and intravenous antibiotics. Currently, after several successful sclerotherapies, the VM-induced coagulopathy is under control, and he is scheduled for surgery to reduce the VM mass (Article IV).

Another severe sclerotherapy complication was also related to severe consumption coagulopathy: a young woman suffered from a VM covering her entire upper limb and axilla. The limb was completely unusable. The VM caused her severe consumption coagulopathy, treated with regular low-molecular-weight heparin injections. The sclerotherapy indications included control of the coagulopathy and facilitation of further surgery to improve the limb's function. The treatment was carefully planned with a haematologist, and sclerotherapy with STS 3% combined with NBCA glue was performed with simultaneous coagulation monitoring. Despite all precautions, after sclerotherapy she developed a multifocal intracerebral haemorrhage, most likely due to the severe and uncontrollable coagulopathy, and died. Neuropathological autopsy revealed no other condition that could have predisposed this patient to such a haemorrhage (Article IV).

9. Discussion

Despite extensive research on the pathogenesis, genetics, risk factors, and treatment of vascular anomalies, many unsolved questions still remain. This study concentrated on the two most common types of vascular anomalies: infantile haemangioma and venous malformation.

9.1. Infantile haemangioma: risk factors, long-term discomfort, and inheritance

Infantile haemangioma most likely has a multifactorial origin. Its main determinants and strongest causative risk factors remain, however, speculative. Studies suggest that the strongest risk factor is low birth weight (46). Other proposed risk factors mainly overlap, and usually occur simultaneously (Table 2). Independent risk factors documented are at least low birth weight and gender (8,9,46,102).

IH risk factors

The figures on maternal gestational diabetes in IH children's mothers are only presented in one study from China (52). Our study population significantly differs from that Chinese cohort. GDM is, however, a common and an increasing pregnancy complication in most western countries (229). GDM occurred more often in our IH cohort's mothers than in the FMBR in our hospital district. Due to differing data sources, we could not conduct a multivariate analysis to segregate independent risk factors; this association therefore remains uncertain. GDM works, however, in opposition to the known IH risk factors, as it usually leads to elevated birth weight, although in some reports it has been linked to preterm delivery (230).

Intrauterine glucose metabolism plays an important role in angiogenesis, because sprouting endothelial cells (ECs) rely for their ATP production mostly on glucose-consuming anaerobic glycolysis (231,232). Diabetic pregnancies could favour this glycolytic activity of ECs in the same manner as hypoxia does, by inducing angio- and vasculogenesis (53,231,233). Additionally, escaping apoptosis is one of the key mechanisms in IH proliferation, because proliferating IH specimens show up-regulation of anti-apoptotic proteins (56,79). Gestational diabetes favours reduced and impaired apoptosis in placental trophoblasts, the potential source of IH stem cells: this process may promote anti-apoptosis and therefore the intrauterine development of IH (56,234). The link between GDM and IH is unclear and requires further study, as this may reveal missing links in the pathogenesis of IH.

IH complications

Even if most IHs resolve without complications and intervention, some lesions can lead to significant and even life-threatening complications necessitating substantial

treatment and resulting in elevated levels of long-term discomfort (102,127,150). In our study, the IH complication rate was 35%, and the intervention rate 37%; these rates are obviously higher than in the general IH population, because we studied a hospital cohort. The predisposing factors for complications and interventions mostly conformed to those previously reported: facial location and segmental and indeterminate IH subtypes are associated with increased risk (102,127). We discovered that preterm birth predisposed the child to ulceration, the most common IH complication. No previous studies show this correlation, but it is relevant for physicians treating IH infants, and may help us to anticipate complications in preterm infants (235,236).

Long-term discomfort resulting from IH

IH-induced long-term discomfort is little studied (150-152). The overall level of long-term discomfort in our study was relatively low, the average for the whole cohort being 2.31 on the VAS scale. This finding is in accordance with earlier findings of quality of life in IH and in non-IH children (151). We found that facial location, segmental but also indeterminate subtypes, history of complication, and intervention caused increased long-term discomfort rates. In contrast, focal and truncal IHs produced lower discomfort rates. Additionally, those IH patients with a first-degree relative with IH also reported elevated discomfort rates compared to rates for sporadic IH cases. Chamlin and colleagues reported decreased quality of life levels for children younger than 19 months with a head and neck IH, or for those undergoing IH-related interventions (150). IH children in our cohort were on average ten years old at the time of the questionnaire, and their IHs had reached full involution. Long-term discomfort assessment is therefore relevant at this age. Future studies will show whether current β-blocker therapies have an effect on long-term outcome and patient satisfaction (126).

Inheritance of IH

Despite the frequency of IHs, its inheritance is relatively little studied, even though one known risk factor is familial clustering (54,85,86,89). Based on our study setting, we are unable to state the true proportion of familial IH cases, but we show that a significant number of IHs involve familial clustering: more than one-third of our patients had a relative with an IH, and one-fourth had a first-degree relative with IH. This rate was somewhat higher than in earlier reports that estimate familial clustering to be present in 10 to 20% of IH cases (8,12). No studies previous to ours have assessed the potential differences between familial and sporadic IHs. We found that familial and sporadic cases were similar in IH characteristics and risk factors, indicating that familial predisposition does not promote any specific IH subtype or localisation. To our knowledge, however, a case of monozygotic twins with IHs in identical location has never been reported before.

To evaluate the true incidence of familial IH remains difficult, because of the nature of IH and its multifactorial origin; some affected family members may actually

represent IH phenocopies, meaning sporadic IHs, because they may have an IH due to risk factors other than familial predisposition (87,91,237). Because of similar features between familial and sporadic IHs, it was impossible to differentiate between these phenocopies. Therefore, further genetic studies are necessary to understand the role of genetic predisposition in IH pathogenesis.

The inheritance pattern of infantile haemangioma in our study mainly followed an autosomal dominant inheritance pattern with incomplete penetrance, supporting earlier findings. Future genetic studies will most likely reveal whether these families also show a linkage to chromosome 5q, as shown by Walter, Blei and colleagues, or show other, possibly angiogenesis-related, germline mutations (54,85,86,89). Additionally, we found families in which the IH may have been maternally transmitted, leading to the question whether the genetic variations could locate in mitochondrial genes. Little is known regarding the role of mitochondria in IH pathogenesis: only one report has studied the mitochondria in IHs, with an emphasis on the mitochondrial apoptotic pathway, important for the involution of IH, but not regarding IH development (238). Of note, neither a mitochondrial nor any other specific disease was observable in these IH children or in their families. Further investigations are required to find the genetic mutations related to IH's familial clustering, and to identify whether they indicate autosomal dominant or maternal transmission.

Limitations of IH studies

Our study was limited to a hospital-based patient cohort representing more difficult IH cases, and this most likely accentuates our complication and intervention rates for IH, as excluding the innocuous IHs followed in primary health care. The questionnaire-based information relies in part on parental recall. However, virtually all pregnancies and newborns are followed in our primary health care system that adheres to national guidelines for pregnancy-related and perinatal data and reports them to the FMBR. Each mother has a personal maternity card containing all data on the course and complications of pregnancy; mothers are therefore well aware of their pregnancy-related data. Tracing the pedigrees of index IH patients with a positive family history was firstly based on the parents' memory. We questioned the IH-affected families first with the written questionnaire and thereafter confirmed this information in detail in the phone interview, where we specifically asked whether the IH of an affected family member had followed the typical clinical course. We were unable to acquire reference data by sending the questionnaire to a randomly selected population because of misuse of the term "haemangioma", which would have produced both false-negative and false-positive cases (5,15,42). Therefore, the reference material regarding perinatal information came from the FMBR, which limited the study.

9.2. Complications of sclerotherapy for venous malformations

The second main objective was to determine treatment complications of sclerotherapy, the most common treatment modality for VMs, by use of a standardized Clavien-Dindo complications classification. These studies revealed that most complications resolve with conservative methods, but severe and even fatal complications may occur. Because we are treating a non-malignant disease, critical assessment of complication risks is vital. The heterogeneity of VM lesions necessitates that the sclerotherapy indication for each patient must be viewed individually.

What is a sclerotherapy complication?

The complication rates of sclerotherapy for VMs range from 0 to 65%, depending on the study setting and complication-reporting threshold (206,208,209,212,217,219,239-255). Most of these studies involve a relatively small patient number and concern ethanol sclerotherapy, which is currently less frequently used, due to its side-effects, or they combine, as we did as well, different sclerosants, which makes the comparison of different studies challenging. Moreover, the definition of a sclerotherapy complication is unclear, as some studies only consider permanent or systemic complications and neglect less severe complications such as prolonged pain, swelling, and ulceration. For example, Berenguer, a pioneer in sclerotherapy treatment, and his colleagues reported acute blistering (50%), very common after sclerotherapy, as a complication, whereas several other studies only report on major complications. Considering these limitations, our complication rates of 17% for head-and-neck and 24% for trunk-and-extremity VMs respectively are generally in accordance with these findings. We report here all adverse events that had been documented in patient records. To date, no consensus exists to differentiate between a sclerotherapy complication and an expected side-effect of the treatment.

Classification of sclerotherapy complications

When evaluating outcomes and complications of any treatment, utilisation of a standardised classification tool is vital: it permits objective comparison among studies and leads eventually to a more robust consensus on any treatment's advantages and disadvantages. To our knowledge, this is the first study that has utilised a standardised classification for sclerotherapy complications. The Clavien-Dindo classification overcomes the use of the subjective terms "minor" and "major" complications, as its grading is based on what further procedures the complication necessitates, rendering the evaluation very objective (214-216). The Clavien-Dindo classification may, however, give a low grading and therefore overlook complications that result in permanent morbidity, such as nerve injuries and prolonged pain, non-curable by any intervention. When the aim of treating VMs is symptom-relief, these types of complications should be taken seriously. In our view, the Clavien-Dindo

classification, despite its weaknesses, represents a more objective complication-grading system than is the SIR grading that categorizes complications as minor or major (213). We propose therefore that the Clavien-Dindo classification is an appropriate candidate to be applied in future studies concerning sclerotherapy complications.

VM characteristics and complication risk

In our studies, VM location was not a significant factor regarding the patient's complication risk. In the head-and-neck cohort, VMs involving the orbit or oral cavity and those lesions penetrating several tissue layers resulted proportionally more often in complications, but due to the small patient number, with no statistically significant difference. A previous study has also addressed the treatment challenge of orbital VMs and shown positive results from pingyanmycin, similar to bleomycin, in sclerotherapy for periorbital lesions, as it causes the least swelling and has therefore fewer side-effects due to the confined location (256). Therefore, VM location should have an impact on sclerosant choice. For a trunk-and-extremity VM patient, location itself was not a determinant factor regarding the complication risk, but subcutaneous VM location was: it predisposed more to skin necrosis than did other tissues. This finding is in accordance with previous findings: subcutaneous VM location is a risk factor for local skin necrosis in sclerotherapy treatment (241,242).

Choice of sclerosant and complication risk

The choice of sclerosant most probably has an impact on complication risk. For trunk and extremity VMs, use of ethanol was linked to higher complication risk and produced mainly local skin necrosis, as also reported earlier (239,241,242). A recent review on different sclerosants agrees with this finding: ethanol produced more skin and neural damages as well as systemic side-effects than did other sclerosants (203). Ethanolamine oleate was reportedly the most efficient sclerosant, but also produced the highest rate of renal and muscle damage. Due to different study settings, outcome, and complication measurements, objective assessment of the efficacy and safety between sclerosants is difficult. The current consensus states, however, that ethanol should be avoided when possible, because of its potentially serious side-effects (202,203). The development of a new gel-like sclerosant, as reported by Schumacher and colleagues, may provide a solution to this issue (207).

Complication mechanisms in sclerotherapy

To avoid complications, it is crucial to understand their potential mechanisms. Sclerosants are toxic agents, targeted at the damage and scarring of endothelial cells (173); sclerosant extravasation outside of the VM causes tissue injury and may lead to adjacent tissue necrosis. Reflux of the sclerosants through capillaries has been reported as a potential complication mechanism (182). This may have been the complication mechanism in our frontal muscle necrosis and maxilla necrosis. Although we used a draining technique to avoid reflux and overfill of the VM, the rise in intraluminal pressure in these cases probably led to extravasation.

Nerve injuries were relatively rare in our studies, and mostly resolved. They are most commonly due to extensive swelling and nerve compression in confined locations (203,257). Post-procedural infections may also occur, even though rarely. In our study of trunk and extremity VMs, the infections were mainly related to therapies in which glue was used to close large venous spaces. As a foreign material, it may have provoked the infection. We therefore now tend to use prophylactic antibiotics for those patients who show pre-existing skin damage or are at risk for developing such damage, or for whom the use of glue as part of the therapy is indicated.

Most of the severe complications related to sclerotherapy resulted from extensive bleedings and blood coagulopathy. The severe bleeding of the tongue VM was uncontrollable by any other methods, making the endovascular management the best available option in this emergency case, which unfortunately resulted in tongue necrosis and sepsis. The patient was on acetylic salicylic acid medication, and had normal coagulation factors, but may have suffered from local coagulopathy in the VM, presumably predisposing to the bleeding. Regarding severe complications for trunk-and-extremity VMs, all patients suffered from serious coagulopathy, which caused most of their complications. Even though VM-related coagulopathy is acknowledged as a known risk factor for complications, no systemic report exists regarding coagulopathy and sclerotherapy (258-260). Any VM-related coagulopathy should therefore be evaluated carefully together with a haematologist, and these VM patients should only be treated in centres prepared to manage potentially life-threatening coagulation and bleeding complications. The sclerotherapy techniques, various scleorsants, and systematic complication- and outcome monitoring deserve a standardised measurement system to improve the safety and efficacy of sclerotherapy for venous malformations.

Limitations of the study

Our research was limited by its retrospective nature, rendering outcome measurement difficult. During the study period of 2007-2013, several varieties of needles, catheters, and vascular access kits have served for sclerotherapy, and the choice of equipment has been tailored for each procedure according to the VM characteristics and to the interventional radiologist's preference. The HUH's vascular anomaly team has set up a patient registry in which we collect all data on vascular anomaly patients and their treatment; this will facilitate further studies and analyses on treatment safety. The relatively low patient number prevented us from observing statistically significant differences in complication risks in relation to VM location, tissue involvement, and sclerosants. However, these studies on head and neck-, and trunk and extremitiy VMs receiving sclerotherapy make up one of the largest studies on this topic conducted to date.

10. Future aspects

The ever-increasing knowledge and understanding of vascular anomalies may in future allow more accurate diagnostics and tailored treatment of vascular anomalies. Infantile haemangioma causes a substantial burden for children, their families, and the healthcare system. Understanding its causative mechanisms may also provide means for prevention. For example, increasing use of non-invasive prenatal testing, which has resulted in a decrease in the number of CVS procedures, one proposed IH risk factor, could have some effect on IH incidence (261).

Despite IH's presumed multifactorial origin, research on its genetic background is essential. Our study on IH inheritance models and identification of families with several affected family members could facilitate future genetic studies. Elucidation of genetic causes will enlarge understanding of the pathogenesis of IH and will facilitate the development of new medical therapies.

The treatment of venous malformations still constitutes an interdisciplinary challenge. Critical evaluation of treatment indication is vital, since not all complications can be avoided. New sclerosants and techniques are constantly developed to obtain better results with minimal complications (207,227). Nevertheless, assessment of VM-related coagulopathy is necessary to avoid any serious side-effects. The increasing use of laser therapy may play a role in VM treatment when sufficient amounts of research data on its efficacy and safety are available (197,223,224,227).

Medical therapy for venous malformations has dramatically evolved: rapamycin, an mTor inhibitor blocking the VM-causative signalling pathway, has been introduced in the treatment of VMs refractory to other treatments (169). It may offer relief for patients with difficult VMs, impossible to treat with other modalities. Future investigations will determine rapamycin's role in VM therapy. A variety of treatment modalities will enable us to combine different therapies to obtain the best possible result for complex VM patients.

11. Conclusions

This study suggests that physicians treating children with infantile haemangiomas should consider the preterm IH infants' higher risk for ulceration, and should especially direct attention to those IHs that result in increased long-term discomfort. Association between maternal gestational diabetes and the child's IH risk is uncertain and calls for further study. In addition to autosomal-dominant transmission in familial IH cases, we propose that some IHs may be maternally transmitted.

Sclerotherapy is rather safe for treatment of venous malformations. Critical evaluation of complications is nevertheless crucial; we found the Clavien-Dindo classification suitable for complication assessment. Sclerotherapy complications do occur but most recover with conservative methods. Complicated VM cases tend to necessitate more sclerotherapies, increasing these patients' complication risk. The use of ethanol as sclerosant should be avoided due to its higher complication risk. VM-related coagulopathy constitutes a significant risk for sclerotherapy and may even lead to fatal complications.

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14. Original publications

Article 1. Risk factors and morbidity of infantile haemangioma: preterm birth promotes ulceration.

Article 2. Inheritance patterns of infantile haemangioma.

Article 3. Complications of sclerotherapy for 75 head and neck venous malformations.

Article 4. Sclerotherapy complications of trunk and extremity venous malformations.